Mohamed, A.
09/766412

FILE 'REGISTRY' ENTERED AT 09:49:36 ON 06 FEB 2004
L1 1108 S (PLASMINOGEN? OR ENDOSTATIN? OR VEGF? OR VASCULAR ENDOT
E "KDR/FLK-1"/CN 5
E "FLK-1/KDR"/CN 5
E "FLK1/KDR"/CN 5
E "KDR/FLK1"/CN 5

FILE 'HCAPLUS' ENTERED AT 09:50:43 ON 06 FEB 2004
L1 1108 SEA FILE=REGISTRY ABB=ON PLU=ON (PLASMINOGEN? OR ENDOSTATIN? OR VEGF? OR VASCULAR ENDOTHELIAL GROWTH FACTOR?)/CN
L2 36818 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR PLASMINOGEN OR PROFIBRINOLYSIN OR PRO FIBRINOLYSIN OR ENDOSTATIN OR VEGF OR VASCULAR ENDOTHELIAL GROWTH OR KDR(A)(FLK1 OR FLKI OR FLK(W)(1 OR I))
L3 5528 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND (ANGIOGEN? OR TUMOR OR TUMOUR OR METAST? OR NEOPLAS? OR CANCER? OR CARCIN?)(5A)(TREAT? OR THERAP? OR PREVENT? OR INHIBIT?)
L4 3090 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND (ANTIANGIOGEN? OR ANTITUMOUR? OR ANTITUMOR? OR ANTIMETAST? OR ANTINEOPLAS? OR ANTICANCER? OR ANTICARCIN?)
L5 185 SEA FILE=HCAPLUS ABB=ON PLU=ON (L3 OR L4) AND ((BOVINE OR COW OR CATTLE)(5A)AORTA OR (CHICKEN OR CHICK)(5A)CHORIOALLANT? OR CAM OR BAEC OR BAE)
L6 20 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND ADMIN?
L7 12 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND (PEPTIDE OR PROTEIN OR POLYPROTEIN OR POLYPEPTIDE OR AMINO)

L7 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:579521 HCAPLUS
DOCUMENT NUMBER: 139:211890
TITLE: **Inhibition** of **Angiogenesis** and **Angiogenesis**-dependent **Tumor** Growth by the Cryptic Kringle Fragments of Human Apolipoprotein(a)
AUTHOR(S): Kim, Jang-Seong; Chang, Ji-Hoon; Yu, Hyun-Kyung; Ahn, Jin-Hyung; Yum, Jung-Sun; Lee, Suk-Keun; Jung, Kyung-Hwan; Park, Doo-Hong; Yoon, Yeup; Byun, Si-Myung; Chung, Soo-Il
CORPORATE SOURCE: Mogam Biotechnology Research Institute, Yongin-city, 449-901, S. Korea
SOURCE: Journal of Biological Chemistry (2003), 278(31), 29000-29008
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Apolipoprotein(a) (apo(a)) contains tandemly repeated kringle domains that are closely related to **plasminogen** kringle 4, followed by a single kringle 5-like domain and an inactive protease-like domain. Recently, the anti-angiogenic activities of apo(a) have been demonstrated both in vitro and in vivo. However, its effects on tumor angiogenesis and the underlying mechanisms involved have not been fully elucidated. To evaluate the anti-angiogenic and anti-tumor activities of the apo(a) kringle domains and to elucidate their mechanism of action, we expressed the last three kringle domains of apo(a), KIV-9, KIV-10, and KV, in

Escherichia coli. The resultant recombinant **protein**, termed rhLK68, exhibited a dose-dependent inhibition of basic fibroblast growth factor-stimulated human umbilical vein endothelial cell proliferation and migration in vitro and inhibited the neovascularization in **chick chorioallantoic** membranes in vivo. The ability of rhLK68 to abrogate the activation of extracellular signal-regulated kinases appears to be responsible for rhLK68-mediated anti-angiogenesis. Furthermore, systemic **administration** of rhLK68 suppressed human lung (A549) and colon (HCT-15) tumor growth in nude mice. Immunohistochem. examination and in situ hybridization anal. of the tumors showed a significant decrease in the number of blood vessels and the reduced expression of **vascular endothelial growth** factor, basic fibroblast growth factor, and angiogenin, indicating that suppression of angiogenesis may have played a significant role in the **inhibition** of **tumor** growth. Collectively, these results suggest that a truncated apo(a), rhLK68, is a potent anti-angiogenic and anti-tumor mol.

IT **127464-60-2, Vascular endothelial growth** factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(decrease in the number of blood vessels and the reduced expression of **vascular endothelial growth** factor, indicating that suppression of angiogenesis may have played a role in the **inhibition** of **tumor** growth)

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:448883 HCAPLUS
DOCUMENT NUMBER: 139:274345
TITLE: Interaction of **plasminogen**-related **protein** B with endothelial and smooth muscle cells in vitro
AUTHOR(S): Morioka, Hideo; Morii, Takeshi; Vogel, Tikva; Hornicek, Francis J.; Weissbach, Lawrence
CORPORATE SOURCE: Orthopaedic Research Laboratories, Massachusetts General Hospital and Harvard Medical School, Boston, MA, 02114, USA
SOURCE: Experimental Cell Research (2003), 287(1), 166-177
CODEN: ECREAL; ISSN: 0014-4827
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Plasminogen**-related **protein** B (PRP-B) closely resembles the N-terminal **plasminogen** activation **peptide**, which is released from **plasminogen** during conversion to plasmin. We have previously demonstrated that the steady-state level of mRNA encoding PRP-B is increased within tumor tissues, and that recombinant PRP-B antagonizes neoplastic growth when **administered** systemically to mice harboring tumors, but no insights into the cell targets of PRP-B have been presented. Employing serum-free medium optimized for culturing human endothelial or smooth muscle cells, we show that recombinant PRP-B inhibits basic fibroblast growth factor-dependent cell migration for

both cell types, as well as tube formation of endothelial cells. Comparison with the **angiogenesis inhibitors** angiostatin and **endostatin** revealed similar results. Recombinant PRP-B is effective in promoting cell attachment of endothelial and smooth muscle cells, and antibody interference expts. reveal that the interaction of recombinant PRP-B with endothelial cells is mediated at least in part by αv-containing integrins. **Inhibition** of **angiogenesis** in vivo by PRP-B was demonstrated in the **chicken chorioallantoic** membrane assay. PRP-B and other **antiangiogenic** mols. may elicit metabolic perturbations in endothelial cells as well as perivascular mesenchymal cells such as smooth muscle cells and pericytes.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:42824 HCAPLUS
DOCUMENT NUMBER: 138:117632
TITLE: Compositions and methods for **inhibiting** endothelial cell proliferation and regulating **angiogenesis** using cancer markers
INVENTOR(S): Holaday, John W.; Fortier, Anne H.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 97 pp., Cont.-in-part of U.S. Ser. No. 907,402.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003012792	A1	20030116	US 2002-131241	20020425
US 6413513	B1	20020702	US 1999-413049	19991006
US 2002137668	A1	20020926	US 2001-907402	20010717
US 6544947	B2	20030408		

PRIORITY APPLN. INFO.:
US 1998-86586P P 19980522
US 1999-316802 A2 19990521
US 1999-413049 A1 19991006
US 2001-907402 A2 20010717

AB The invention provides cancer markers including prostate specific antigen (PSA), carcinoembryonic antigen (CEA), neuron specific enolase (NSE), human chorionic gonadotropin (HCG-α, HCG-β), cancer antigen (CA 19-9), analogs, derivs., variants, substantially homologous **peptides**, mimetics, agonists, antagonists, or fusion **peptides** of these cancer markers. In a preferred embodiment of the invention, the cancer marker is **administered** with an **angiogenic inhibitory peptide**, a cytotoxic drug or both. Serine proteases and kallikreins exhibit potent **antiangiogenic** activity on human and other animal cells, particularly endothelial cells. More particularly, the use of a cancer marker, such as PSA, CEA, HCG, NSE, or CA19-9, to **inhibit** or ameliorate **angiogenesis** and **angiogenesis**-related diseases such as cancer, arthritis, macular degeneration, and diabetic

retinopathy is disclosed.

IT **127464-60-2, Vascular endothelial growth** factor **187888-07-9, Endostatin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. and methods for **inhibiting** endothelial cell proliferation and regulating **angiogenesis** using cancer markers)

L7 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:942219 HCAPLUS
DOCUMENT NUMBER: 138:215006
TITLE: Domain swapping in a COOH-terminal fragment of platelet factor 4 generates potent **angiogenesis inhibitors**
AUTHOR(S): Hagedorn, Martin; Zilberberg, Lior; Wilting, Jorg; Canron, Xavier; Carrabba, Giorgio; Giussani, Carlo; Pluderi, Mauro; Bello, Lorenzo; Bikfalvi, Andreas
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale EMI 0113 Molecular Mechanisms of Angiogenesis, Universite de Bordeaux I, Talence, 33405, Fr.
SOURCE: Cancer Research (2002), 62(23), 6884-6890
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A few **peptide** residues in structurally important locations often determine biol. functions of **proteins** implicated in the regulation of angiogenesis. We have shown recently that the short COOH-terminal segment PF-447-70 derived from platelet factor 4 (PF-4) is the smallest sequence that conserves potent **antiangiogenic** activity in vitro and in vivo. Here we show that modified COOH-terminal PF-4 **peptides** containing the sequence ELR (or related DLR), a critical domain present in proangiogenic chemokines, surprisingly elicit several times greater **antiangiogenic** potential than the original **peptide** . The modified **peptides** inhibit binding of iodinated **vascular endothelial growth** factor and fibroblast growth factor 2 to endothelial cell receptors, endothelial cell proliferation, migration, and microvessel assembly in the rat aortic ring model at lower doses than PF-447-70. On the differentiated **chick chorioallantoic** membrane, topical application of 40 μg of modified **peptides** potently reduces capillary angiogenesis induced by **vascular endothelial growth** factor165, a dose where **peptide** PF-447-70 was inactive. Established intracranial glioma in nude mice decreased significantly in size when treated locally with a total dose of 250 μg of **peptide** PF-447-70DLR (n = 10) compared with the same dose of the original PF-447-70 **peptide** (n = 10) or controls (n = 30). Tailored PF-4 **peptides** represent a new class of **antiangiogenic** agents with a defined mode of action and a strong in vivo activity.

IT **127464-60-2, Vascular endothelial growth** factor
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)

(165 isoform; C-terminal fragment of platelet factor 4 inhibits **VEGF** and FGF-2 induced endothelial cell proliferation, migration, and microvessel assembly)
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:754234 HCAPLUS
DOCUMENT NUMBER: 137:257639
TITLE: Histidine-rich glycoprotein **polypeptides** use for **inhibition** of **angiogenesis**
INVENTOR(S): Welsh, Lena Claesson; Larsson, Helena; Olsson, Anna-Karin
PATENT ASSIGNEE(S): Innoventus Project AB, Swed.
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002076486	A2	20021003	WO 2002-IB2425	20020204
WO 2002076486	A3	20030417		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002165131	A1	20021107	US 2002-67093	20020204
EP 1357930	A2	20031105	EP 2002-733167	20020204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2001-266505P P 20010205
WO 2002-IB2425 W 20020204

AB The invention relates to histidine-rich glycoprotein (HRGP) **polypeptides** and the use of these **polypeptides**. The invention includes methods for the **inhibition** of **angiogenesis** by **administering** an HRGP **polypeptide**. The invention also includes pharmaceutical compns. and articles of manufacture comprising HRGP **polypeptides**, antibodies and receptors that bind to an HRGP **polypeptide**, HRGP-depleted plasma and polynucleotides, vectors and host cells that encode HRGP **polypeptides**.

IT **187888-07-9, Endostatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(histidine-rich glycoprotein **polypeptides** use for **inhibition** of **angiogenesis**)

L7 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:575742 HCAPLUS
DOCUMENT NUMBER: 137:135089
TITLE: Small **peptides** having anti-**angiogenic** and endothelial cell **inhibition** activity
INVENTOR(S): Ge, Ruowen; Kini, R. Manjunatha
PATENT ASSIGNEE(S): Singapore
SOURCE: U.S. Pat. Appl. Publ., 24 pp., Cont.-in-part of U.S. 6,200,954.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002103129	A1	20020801	US 2001-766412	20010122
US 6200954	B1	20010313	US 1999-385442	19990830
PRIORITY APPLN. INFO.:			US 1998-99313P P	19980904
			US 1999-385442 A2	19990830

AB The invention provides **peptides** having potent anti-**angiogenic** activity and endothelial cell proliferation **inhibition** activity. The **peptides** can be **administered** as pharmaceutical compns. for **prevention** or **treatment** of undesired **angiogenesis**, e.g. for **prevention** of **tumor metastasis** or **inhibition** of primary **tumor** growth.
IT **9001-91-6, Plasminogen 127464-60-2, Vascular endothelial growth** factor **141350-03-0**, Flt-1 kinase **150977-45-0, Flk-1/KDR VEGF** receptor tyrosine kinase **187888-07-9, Endostatin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**peptide** derived from; **peptides** with anti-**angiogenic** and endothelial cell **inhibition** activity)

L7 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:390205 HCAPLUS
DOCUMENT NUMBER: 137:304666
TITLE: Angiogenic activity of β-sitosterol in the ischaemia/reperfusion-damaged brain of Mongolian gerbil
AUTHOR(S): Choi, Seongwon; Kim, Kyu-Won; Choi, Jae-Sue; Han, Sang-Taek; Park, Young-In; Lee, Seung-Ki; Kim, Jeong-Soon; Chung, Myung-Hee
CORPORATE SOURCE: Department of Pharmacology, Seoul National University College of Medicine, Seoul, 110-799, S. Korea
SOURCE: Planta Medica (2002), 68(4), 330-335
CODEN: PLMEAA; ISSN: 0032-0943
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aloe vera continues to be used for wound healing as a folk medicine. We previously reported that A. vera gel has angiogenic activity. In this study, we report upon the isolation of an angiogenic component β-sitosterol from A. vera and examination of its effect upon damaged blood vessels of the Mongolian gerbil. In a **chick** embryo **chorioallantoic** membrane assay, β-sitosterol was found to have an angiogenic effect. It enhanced new vessel formation in gerbil brains damaged by ischemia/reperfusion, especially in the cingulate cortex and septal regions, in a dose-dependent fashion (up to 500 μg/kg, $p < 0.05$, $n = 34-40$). β-Sitosterol also enhanced the expressions of **proteins** related to angiogenesis, namely von Willebrand factors, **vascular endothelial growth** factor (**VEGF**), **VEGF** receptor Flk-1, and blood vessel matrix laminin ($p < 0.05$, $n = 6$). In addition, the i.p. **administration** of β-sitosterol at 500 μg/kg/day for a period of 19 days significantly improved the motion recovery of ischemia/reperfusion-damaged gerbils as assessed by rota-rod testing ($p < 0.001$, $n = 10$). Our results suggest that β-sitosterol has **therapeutic angiogenic** effects on damaged blood vessels.

IT **127464-60-2, Vascular endothelial growth** factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(angiogenic activity of β-sitosterol in ischemia/reperfusion-damaged brain of Mongolian gerbil)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:752361 HCAPLUS
DOCUMENT NUMBER: 136:17108
TITLE: p22 Is a Novel **Plasminogen** Fragment with **Antiangiogenic** Activity
AUTHOR(S): Kwon, Mijung; Yoon, Chang-Soon; Fitzpatrick, Sandra; Kassam, Geetha; Graham, Kenneth S.; Young, Mary K.; Waisman, David M.
CORPORATE SOURCE: Cancer Biology Research Group Departments of Biochemistry & Molecular Biology and Oncology, University of Calgary, Calgary, AB, T2N 4N1, Can.
SOURCE: Biochemistry (2001), 40(44), 13246-13253
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tumor or tumor-associated cells cleave circulating **plasminogen** into three or four kringle-containing **antiangiogenic** fragments, collectively referred to as angiostatin. Angiostatin blocks **tumor** growth and **metastasis** by **preventing** the growth of endothelial cells that are critical for tumor vascularization. Here, we show that cancer and normal cells convert **plasminogen** into a novel 22 kDa fragment (p22). Production of this **plasminogen** fragment in a cell-free system has allowed characterization of the structure and activity of the **protein**. The p22 consists of **amino** acid residues 78-180 of **plasminogen** and therefore embodies the first **plasminogen** kringle (residues 84-162) as well as

addnl. N- and C-terminal residues. CD and intrinsic fluorescence spectrum anal. have defined structural differences between p22 and recombinant **plasminogen** kringle 1 (rK1), therefore suggesting a unique conformation for kringle 1 within p22. Proliferation of capillary endothelial cells but not cells of other lineages was selectively inhibited by p22 in vitro. In addition, p22 prevented vascular growth of **chick chorioallantoic** membranes (**CAMs**) in vivo. Furthermore, **administration** of p22 at low dose suppressed the growth of murine Lewis lung carcinoma (LLC) metastatic foci in vivo. This is the first identification of a single kringle-containing **antiangiogenic plasminogen** fragment produced under physiol. conditions.

IT **9001-91-6, Plasminogen**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p22 is a novel **plasminogen** fragment with **antiangiogenic** activity)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:489619 HCAPLUS
DOCUMENT NUMBER: 135:71268
TITLE: Use of locked nucleic acid-modified oligonucleotides for **treatment** of **cancer** and inflammation
INVENTOR(S): Orum, Henrik; Koch, Troel; Skouv, Jan; Jakobsen, Mogen Havsteen
PATENT ASSIGNEE(S): Exiqon A/S, Den.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001048190	A2	20010705	WO 2000-IB2043	20001222
WO 2001048190	A3	20020510		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002068709	A1	20020606	US 2000-747913	20001222
EP 1240322	A2	20020918	EP 2000-990866	20001222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

JP 2003524637 T2 20030819 JP 2001-548703 20001222
PRIORITY APPLN. INFO.: US 1999-171873P P 19991223
WO 2000-IB2043 W 20001222

AB The invention relates to therapeutic applications of LNA-modified oligonucleotides. In particular, the invention provides methods for treatment of undesired cell growth as well as treatment of inflammatory related diseases and disorders. Preferably, **administration** of an LNA-modified oligonucleotide modulates expression of a targeted gene associated with the undesired cell growth or an inflammatory related disease or disorder. Thus, the peritoneal cells of rats injected i.p. with LNA-containing oligonucleotides directed to FcεR1α mRNA produced less FcεR1α and released less histamine than did rats given unmodified oligonucleotides.

L7 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:185777 HCAPLUS
DOCUMENT NUMBER: 134:217187
TITLE: Small **peptides** having potent anti-angiogenic activity
INVENTOR(S): Ge, Rowen; Kini, R. Manjunatha
PATENT ASSIGNEE(S): National University of Singapore, Singapore
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001018030	A2	20010315	WO 2000-SG131	20000901
WO 2001018030	A3	20010927		
W: CN, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
SG 87828	A1	20020416	SG 1999-4310	19990903

PRIORITY APPLN. INFO.: SG 1999-4310 A 19990903

AB The present invention provides **peptides** having potent anti-angiogenic activity. The **peptides** can be **administered** as pharmaceutical compns. for **prevention** or **treatment** of undesired **angiogenesis**, for instance for **prevention** of **tumor metastasis** or **inhibition** of primary **tumor** growth.

IT **9001-91-6, Plasminogen 127464-60-2, Vascular endothelial growth** factor **187888-07-9, Endostatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragments; small **peptides** having potent anti-angiogenic activity)

L7 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:879152 HCAPLUS
DOCUMENT NUMBER: 134:172781
TITLE: HGF/NK4, a four-kringle antagonist of hepatocyte

growth factor, is an **angiogenesis inhibitor** that suppresses **tumor** growth and **metastasis** in mice

AUTHOR(S): Kuba, Keiji; Matsumoto, Kunio; Date, Kazuhiko; Shimura, Hideo; Tanaka, Masao; Nakamura, Toshikazu

CORPORATE SOURCE: Division of Biochemistry, Department of Oncology, Biomedical Research Center, Osaka University Medical School, Suita, 565-0871, Japan

SOURCE: Cancer Research (2000), 60(23), 6737-6743
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We reported that NK4, composed of the N-terminal hairpin and subsequent four kringle domains of hepatocyte growth factor (HGF), acts as the competitive antagonist for HGF. We now provide the first evidence that NK4 **inhibits tumor** growth and **metastasis** as an **angiogenesis inhibitor** as well as an HGF antagonist. **Administration** of NK4 suppressed primary tumor growth and lung metastasis of Lewis lung carcinoma and Jyg-MC(A) mammary carcinoma s.c. implanted into mice, although neither HGF nor NK4 affected proliferation and survival of these tumor cells in vitro. NK4 treatment resulted in a remarkable decrease in microvessel d. and an increase of apoptotic tumor cells in primary **tumors**, which suggests that the **inhibition** of primary **tumor** growth by NK4 may be achieved by suppression of tumor angiogenesis. In vivo, NK4 **inhibited angiogenesis** in **chick chorioallantoic** membranes and in rabbit corneal neovascularization induced by basic fibroblast growth factor (bFGF). In vitro, NK4 inhibited growth and migration of human microvascular endothelial cells induced by bFGF and **vascular endothelial growth** factor (**VEGF**) as well as by HGF. HGF and **VEGF** activated the Met/HGF receptor and the KDR/**VEGF** receptor, resp., whereas NK4 inhibited HGF-induced Met tyrosine phosphorylation but not **VEGF**-induced KDR phosphorylation. NK4 inhibited HGF-induced ERK1/2 (p44/42 mitogen-activated **protein** kinase) activation, but allowed for bFGF- and **VEGF**-induced ERK1/2 activation. These results indicate that NK4 is an **angiogenesis inhibitor** as well as an HGF antagonist, and that the **antiangiogenic** action of NK4 is independent of its activity as HGF antagonist. The bifunctional properties of NK4 to act as an **angiogenesis inhibitor** and as an HGF antagonist raises the possibility that NK4 may prove **therapeutic** for **cancer** patients.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:573686 HCAPLUS

DOCUMENT NUMBER: 133:176175

TITLE: Methods for **treatment** of **tumors** and **metastases** using a combination of anti-angiogenic and

immunotherapies

INVENTOR(S): Lode, Holger N.; Reisfeld, Ralph A.; Cheresh, David A.; Gillies, Stephen D.

PATENT ASSIGNEE(S): The Scripps Research Institute, USA; Lexigen Pharmaceuticals Corporation

SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000047228	A1	20000817	WO 2000-US3483	20000211
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2360106	AA	20000817	CA 2000-2360106	20000211
EP 1156823	A1	20011128	EP 2000-910138	20000211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008161	A	20020528	BR 2000-8161	20000211
JP 2002536419	T2	20021029	JP 2000-598179	20000211
ZA 2001006455	A	20021106	ZA 2001-6455	20010806
NO 2001003906	A	20011009	NO 2001-3906	20010810

PRIORITY APPLN. INFO.: US 1999-119721P P 19990212
WO 2000-US3483 W 20000211

AB The invention teaches methods for **treating tumors** and **tumor metastases** in a mammal comprising **administering**, to a mammal in need of treatment, a therapeutic amount of an antagonist sufficient to **inhibit angiogenesis** in combination with a **therapeutic** amount of anti-**tumor** immunotherapeutic agent, such as an anti-tumor antigen antibody/cytokine fusion **protein** having a cytokine and a recombinant Ig **polypeptide** chain sufficient to elicit a cytokine-specific biol. response.

IT **127464-60-2, Vascular endothelial growth** factor
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-**angiogenic** and **antitumor** agents for **treatment** of **tumors** and **metastases**)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 10:10:08 ON 06 FEB 2004)

L8 58 S L7

L9 37 DUP REM L8 (21 DUPLICATES REMOVED)

L9 ANSWER 1 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-513460 [48] WPIDS
CROSS REFERENCE: 2003-393513 [37]
DOC. NO. CPI: C2003-137393
TITLE: New multivalent, monospecific binding **protein** comprising two or more binding sites having affinity for the same single target antigen, where each binding site is associated with scFv fragments, useful for diagnosing or **treating tumor.**
DERWENT CLASS: B04 D16
INVENTOR(S): CHANG, C K; GOLDENBERG, D M; ROSSI, E
PATENT ASSIGNEE(S): (CHAN-I) CHANG C K; (GOLD-I) GOLDENBERG D M; (ROSS-I) ROSSI E
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003033654	A2	20030424	(200348)*	EN	62

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

US 2003148409 A1 20030807 (200358)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003033654	A2	WO 2002-US32718	20021015
US 2003148409	A1 Provisional	US 2001-328835P	20011015
	Provisional	US 2001-341881P	20011221
	Provisional	US 2002-345641P	20020108
	Provisional	US 2002-404919P	20020822
		US 2002-270073	20021015

PRIORITY APPLN. INFO: US 2002-404919P 20020822; US 2001-328835P 20011015; US 2001-341881P 20011221; US 2002-345641P 20020108; US 2002-270073 20021015
AN 2003-513460 [48] WPIDS
CR 2003-393513 [37]
AB WO2003033654 A UPAB: 20030910
NOVELTY - A multivalent, monospecific binding **protein** comprising two or more binding sites having affinity for the same single target antigen, where the binding sites are formed by the association of two or more single chain Fv (scFV) fragments, and each scFV fragment comprises at least two variable domains derived from a humanized or human monoclonal antibody, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) an expression vector comprising a nucleotide sequence encoding the monospecific diabody, triabody or tetrabody;

(2) a host cell comprising the expression vector;

(3) diagnosing the presence of a tumor by **administering** to a subject suspected of having a tumor a detectable amount of the binding **protein**, and monitoring the subject to detect any binding of the binding **protein** to tumor;

(4) delivering one or more diagnostic and/or **therapeutic** agents to a **tumor** by **administering** the binding **protein** to the subject; and

(5) a kit for therapeutic and/or diagnostic use, comprising the binding **protein**, and additional reagents, equipments and instructions for use.

ACTIVITY - Cytostatic. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The binding **proteins** are useful for diagnosing and **treating tumors**, e.g. **carcinoma**, a melanoma, a sarcoma, a neuroblastoma, a leukemia, a glioma, a lymphoma and a myeloma; or a cancer selected from acute lymphoblastic leukemia, acute myelogenous leukemia, biliary, breast, cervical, chronic lymphocytic leukemia, chronic myelogenous leukemia, colorectal, endometrial, esophageal, gastric, head and neck, Hodgkin's lymphoma, lung, medullary thyroid, non-Hodgkin's lymphoma, ovarian, pancreatic, prostate and urinary bladder. When **treating** a **tumor** by **administering** to the subject the binding **protein**, and/or a therapeutic agent , the therapeutic agent is a chemotherapeutic drug, a toxin, external radiation, brachytherapy radiation agent, a radiolabeled **protein**, an **anticancer** drug, or an **anticancer** antibody (all claimed).

Dwg.0/4

L9 ANSWER 2 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2003-393499 [37] WPIDS

DOC. NO. CPI: C2003-104602

TITLE: New nucleic acid constructs comprising a region encoding a chimeric **polypeptide** fused to an apoptosis signaling molecule, and a region encoding an element directing **polypeptide** expression, useful for down-regulating angiogenesis.

DERWENT CLASS: B04 D16

INVENTOR(S): GREENBERGER, S; HARATS, D

PATENT ASSIGNEE(S): (VASC-N) VASCULAR BIOGENICS LTD

COUNTRY COUNT: 100

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003033514	A1	20030424	(200337)*	EN	23

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003033514 A1		WO 2002-IL339	20020501

PRIORITY APPLN. INFO: US 2001-330118P 20011019
AN 2003-393499 [37] WPIDS
AB WO2003033514 A UPAB: 20030612
NOVELTY - A new nucleic acid construct (I) comprising:
(a) a first polynucleotide region encoding a chimeric **polypeptide** including a ligand binding domain fused to an effector domain of an apoptosis signaling molecule; and
(b) a second polynucleotide region encoding a cis acting regulatory element binding for directing the expression of the chimeric **polypeptide** in a specific tissue or cell, is new.
DETAILED DESCRIPTION - A new nucleic acid construct (I) comprising:
(a) a first polynucleotide region encoding a chimeric **polypeptide** including a ligand binding domain fused to an effector domain of an apoptosis signaling molecule; and
(b) a second polynucleotide region encoding a cis acting regulatory element binding for directing the expression of the chimeric **polypeptide** in a specific tissue or cell, is new.
The ligand-binding domain is selected such that it is capable of binding a ligand present in the specific tissue or cell, while binding of the ligand to the ligand-binding domain activates the effector domain of the apoptosis-signaling molecule.
INDEPENDENT CLAIMS are also included for:
(1) a mammalian cell transformed with (I);
(2) a method of down regulating angiogenesis in a tissue of a subject by **administering** (I), which is designed and configured for generating apoptosis in a subpopulation of angiogenic cells;
(3) a pharmaceutical composition for down regulating angiogenesis in a tissue of a subject, comprising as an active ingredient a nucleic acid construct (I) designed and configured for generating apoptosis in a subpopulation of angiogenic cells, and a pharmaceutical carrier;
(4) a method of treating a disease or condition associated with excessive neovascularization by **administering** the nucleic acid construct (I) designed and configured for generating apoptosis in a sub-population of angiogenic cells; and
(5) a method of **treating** a **tumor** in a subject by **administering** the nucleic acid construct (I) designed and configured for generating apoptosis in tumor cells.
ACTIVITY - Cytostatic.
The ability of Ad-PPE-Fas chimera to induce apoptosis of endothelial cells was determined. Pre-proendothelin directed adenovirus-mediated transduction of endothelial cells resulted in an evident and massive cell death. HUVEC and **BAEC** infected with Ad-PPE-Fas had morphological features of adherent cells undergoing apoptosis including membrane blebbing, rounding and shrinking, and detachment from the culture dish. Assessment of cytotoxic properties of Ad-PPE-Fas-c was effected by expressing this virus in cells expressing the reporter gene GFP under the control of the PPE-1 promoter. Most of the transduced cells acquired a typical apoptotic appearance 72 hours post-transduction, while cells co-transduced with control virus and Ad-PPE-GFP appeared normal.

MECHANISM OF ACTION - Gene therapy.
USE - The nucleic acid constructs are useful for down-regulating angiogenesis in specific tissue regions of a subject, and for activating apoptosis in specific cell subsets for the **treatment** of **tumors** or diseases characterized by excessive or aberrant neovascularization or cell growth.
Dwg.0/16

L9 ANSWER 3 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-801241 [75] WPIDS
DOC. NO. NON-CPI: N2003-642063
DOC. NO. CPI: C2003-221209
TITLE: **Inhibiting angiogenesis**, especially for **treating tumors**, comprises **administration** of endorepellin **protein** or its fragments, derivatives, or analogs.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): IOZZO, R V
PATENT ASSIGNEE(S): (IOZZ-I) IOZZO R V; (UYJE-N) UNIV JEFFERSON THOMAS
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003104999	A1	20030605	(200375)*		34
WO 2003048333	A2	20030612	(200375)	EN	

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003104999	A1	US 2001-6011	20011204
WO 2003048333	A2	WO 2002-US38742	20021204

PRIORITY APPLN. INFO: US 2001-6011 20011204
AN 2003-801241 [75] WPIDS
AB US2003104999 A UPAB: 20031120
NOVELTY - **Inhibiting** (M1a) **angiogenesis** in a (**tumor** of a) patient, by **administering** into a tissue or organ an endorepellin **protein**, or its fragments, derivatives or analogs to inhibit generation of blood vessels, is new. The endorepellin **protein** has an **amino** acid sequence of domain V of perlecan.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) monitoring (M2) an angiogenesis-mediated disease or condition in a patient by measuring an amount of endorepellin **protein**, or its fragments or derivatives or analogs in a

sample in which an increase in the amount of endorepellin **protein** relative to that present in a sample derived from the patient at an earlier time indicates disease progression, and a decrease in the amount indicates disease regression;

(2) **treating** (M1b) an **angiogenesis**-mediated disease (especially a tumor) in a patient, by **administering** an endorepellin **protein**, its fragments or derivatives or analogs, to induce disease regression;

(3) **treating** (M1c) an **angiogenesis**-mediated disease (especially a tumor) in a patient by **administering** a conventional therapeutic regimen and an endorepellin **protein**, or its fragments, derivatives, or analogs, and then discontinuing the conventional therapy while continuing the endorepellin treatment so that regression is induced (especially to extend dormancy of **metastases** and **inhibit tumor** growth);

(4) a diagnostic kit for the detection or measurement of endorepellin **protein**, its fragments or derivatives or analogs in a sample from a patient, comprising an endorepellin specific antibody; and

(5) a pharmaceutical composition comprising an endorepellin **protein**, its fragments or derivatives or analogs and a carrier or excipient.

ACTIVITY - Cytostatic; Antiarteriosclerotic; Vasotropic; Antiinflammatory; Vulnerary; Antipsoriatic; Thrombolytic; Ophthalmological; Gynecological; Contraceptive.

MECHANISM OF ACTION - **Angiogenesis inhibitor** ; **Antimetastatic**.

Endorepellin blocked the angiogenic activity of **vascular endothelial growth** factor (**VEGF**) as determined by the **chicken chorioallantoic** membrane (**CAM**) assay. Human umbilical vein endothelial cell (HUVEC) migration was **inhibited**, with a subsequent decrease in **angiogenesis** in vivo. In the presence of **VEGF**, the characteristic spoke wheel-like vessel formation was induced towards the sponge. In the presence of endorepellin, the vessel sprouts were markedly reduced to a level comparable to the negative control.

USE - The **treatment** methods are useful for **inhibiting angiogenesis** in the **treatment** of **angiogenesis** related diseases or conditions, and especially cancers. M2 is useful for monitoring an angiogenesis related disease or condition (all claimed). Diseases or conditions other than **cancers** that may be **treated** include atherosclerosis, vascular restenosis, neointima formation following vascular trauma, fibrosis associated with a chronic inflammatory condition, lung fibrosis, wound scarring, psoriasis, deep venous thrombosis, corneal diseases, ovulation, menstruation, and placentation.

ADVANTAGE - The endorepellin produces an inhibitory effect on cell migration and invasion extending the dormancy of micrometastases and inhibiting the growth of any residual primary tumor.

Dwg.0/5

L9 ANSWER 4 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003370875 EMBASE

TITLE: Structure and **inhibitory** effects on **angiogenesis** and **tumor** development of a new **vascular endothelial growth** inhibitor.

AUTHOR: Zilberberg L.; Shinkaruk S.; Lequin O.; Rousseau B.; Hagedorn M.; Costa F.; Caronzolo D.; Balke M.; Canron X.; Convert O.; Lain G.; Gionnet K.; Goncalves M.; Bayle M.; Bello L.; Chassaing G.; Deleris G.; Bikfalvi A.

CORPORATE SOURCE: A. Bikfalvi, INSERM E 0113, Molecular Angiogenesis Laboratory, Universite de Bordeaux 1, 33405 Talence, France. a.bikfalvi@croissance.u-bordeaux.fr

SOURCE: Journal of Biological Chemistry, (12 Sep 2003) 278/37 (35564-35573).
Refs: 67
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Blocking **angiogenesis** is an attractive strategy to **inhibit tumor** growth, invasion, and **metastasis**. We describe here the structure and the biological action of a new cyclic **peptide** derived from **vascular endothelial growth** factor (**VEGF**). This 17-**amino** acid molecule designated cyclopeptidic **vascular endothelial growth** inhibitor (cyclo-VEGI, CBO-P11) encompasses residues 79-93 of **VEGF** which are involved in the interaction with **VEGF** receptor-2. In aqueous solution, cyclo-VEGI presents a propensity to adopt a helix conformation that was largely unexpected because only β-sheet structures or random coil conformations have been observed for macrocyclic **peptides**. Cyclo-VEGI inhibits binding of iodinated **VEGF**(165) to endothelial cells, endothelial cells proliferation, migration, and signaling induced by **VEGF**(165). This **peptide** also exhibits anti-angiogenic activity in vivo on the differentiated **chicken chorioallantoic** membrane. Furthermore, cyclo-VEGI significantly blocks the growth of established intracranial glioma in nude and syngeneic mice and improves survival without side effects. Taken together, these results suggest that cyclo-VEGI is an attractive candidate for the development of novel **angiogenesis inhibitor** molecules useful for the **treatment** of **cancer** and other **angiogenesis** -related diseases.

L9 ANSWER 5 OF 37 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003351019 MEDLINE
DOCUMENT NUMBER: 22765579 PubMed ID: 12746434
TITLE: **Inhibition** of **angiogenesis** and **angiogenesis**-dependent **tumor** growth by the cryptic kringle fragments of human apolipoprotein(a).
AUTHOR: Kim Jang-Seong; Chang Ji-Hoon; Yu Hyun-Kyung; Ahn Jin-Hyung; Yum Jung-Sun; Lee Suk-Keun; Jung

Kyung-Hwan; Park Doo-Hong; Yoon Yeup; Byun Si-Myung; Chung Soo-Il
CORPORATE SOURCE: Mogam Biotechnology Research Institute, Yongin-city, Kyonggi-do 449-910, Korea.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2003 Aug 1) 278 (31) 29000-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030729
Last Updated on STN: 20030911
Entered Medline: 20030910

AB Apolipoprotein(a) (apo(a)) contains tandemly repeated kringle domains that are closely related to **plasminogen** kringle 4, followed by a single kringle 5-like domain and an inactive protease-like domain. Recently, the anti-angiogenic activities of apo(a) have been demonstrated both in vitro and in vivo. However, its effects on tumor angiogenesis and the underlying mechanisms involved have not been fully elucidated. To evaluate the anti-angiogenic and anti-tumor activities of the apo(a) kringle domains and to elucidate their mechanism of action, we expressed the last three kringle domains of apo(a), KIV-9, KIV-10, and KV, in Escherichia coli. The resultant recombinant **protein**, termed rhLK68, exhibited a dose-dependent inhibition of basic fibroblast growth factor-stimulated human umbilical vein endothelial cell proliferation and migration in vitro and inhibited the neovascularization in **chick chorioallantoic** membranes in vivo. The ability of rhLK68 to abrogate the activation of extracellular signal-regulated kinases appears to be responsible for rhLK68-mediated anti-angiogenesis. Furthermore, systemic **administration** of rhLK68 suppressed human lung (A549) and colon (HCT-15) tumor growth in nude mice. Immunohistochemical examination and in situ hybridization analysis of the tumors showed a significant decrease in the number of blood vessels and the reduced expression of **vascular endothelial growth** factor, basic fibroblast growth factor, and angiogenin, indicating that suppression of angiogenesis may have played a significant role in the **inhibition** of **tumor** growth. Collectively, these results suggest that a truncated apo(a), rhLK68, is a potent anti-angiogenic and anti-tumor molecule.

L9 ANSWER 6 OF 37 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 2

ACCESSION NUMBER: 2003:550875 BIOSIS
DOCUMENT NUMBER: PREV200300553648
TITLE: **Inhibition** of **angiogenesis** by non-toxic doses of temozolomide.
AUTHOR(S): Kurzen, Hjalmar [Reprint Author]; Schmitt, Stefan; Naeher, Helmut; Moehler, Thomas
CORPORATE SOURCE: Department of Dermatology, University of Heidelberg, Voss-Strassse 2, 69115, Heidelberg, Germany
Hjalmar_Kurzen@med.uni-heidelberg.de
SOURCE: Anti-Cancer Drugs, (August 2003) Vol. 14, No. 7, pp. 515-522. print.

CODEN: ANTDEV. ISSN: 0959-4973.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Nov 2003
Last Updated on STN: 26 Nov 2003

AB It is well established that certain chemotherapeutic agents have potent **antiangiogenic** properties which may be part of their **antitumor** activity. Temozolomide (TMZ) is a lipophilic methylating agent used in the **therapy** of malignant melanoma and other **tumors**. We sought to determine whether TMZ is capable of **inhibiting angiogenesis** or influencing endothelial function. We used the in vivo chorioallantoic membrane (**CAM**) assay, and HUVEC-based in vitro Matrigel, adhesion and proliferation assays to determine the **antiangiogenic** effects of different doses of TMZ. In the **CAM** assay, **angiogenesis** was significantly **inhibited** by 5 muM TMZ, a concentration also found to be effective in interfering with in vitro angiogenesis as measured by the Matrigel assay. For the inhibition of basic fibroblast growth factor (bFGF)-, **vascular endothelial growth** factor (**VEGF**)- or beta-phorbol 12-myristate-13-acetate (PMA)-induced endothelial cell proliferation or endothelial cell adhesion to fibronectin, TMZ concentrations of at least 25 muM were necessary, indicating that bFGF-, **VEGF**- or **protein** kinase C-mediated pathways may not primarily be involved in the observed **antiangiogenic** effect. Thus, we could demonstrate that TMZ **inhibits angiogenesis** at low, non-toxic doses that correspond to the plasma concentrations achieved by an oral application of 20 mg/m2 every 8 h. This 'metronomic' scheduling has already been used in phase I studies and has produced **antitumor** effects. Therefore, the **antitumor** activity of TMZ may, at least in part, be due to its **antiangiogenic** properties. The precise mechanism of its **antiangiogenic** action remains to be elucidated.

L9 ANSWER 7 OF 37 MEDLINE on STN
ACCESSION NUMBER: 2003097023 MEDLINE
DOCUMENT NUMBER: 22496824 PubMed ID: 12610518
TITLE: A novel hypoxia-dependent 2-nitroimidazole KIN-841 **inhibits tumour**-specific **angiogenesis** by blocking production of angiogenic factors.
AUTHOR: Shimamura M; Nagasawa H; Ashino H; Yamamoto Y; Hazato T; Uto Y; Hori H; Inayama S
CORPORATE SOURCE: Medical R&D Center, The Tokyo Metropolitan Institute of Medical Science, Japan.. mshima@rinshoken.or.jp
SOURCE: BRITISH JOURNAL OF CANCER, (2003 Jan 27) 88 (2) 307-13.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030302
Last Updated on STN: 20030326
Entered Medline: 20030325

AB Tumour angiogenesis is initiated by angiogenic factors that are produced in large amounts by hypoxic tumour cells. The inhibition of this step may lead to tumour-specific **antiangiogenesis** because normal tissues are not usually hypoxic. On the other hand, blocking a biological function of endothelial cells is known to result in **angiogenic inhibition**. To produce a tumour-specific and powerful **antiangiogenesis**, we determined whether potent **angiogenic inhibition** could be achieved by **inhibiting** the production of **angiogenic** factors by hypoxic tumour cells and simultaneously blocking certain angiogenic steps in endothelial cells under normoxia. We focused on the 2-nitroimidazole moiety, which is easily incorporated into hypoxic cells and exhibits its cytotoxicity as hypoxic cytotoxin. We designed and synthesised 2-nitroimidazole derivatives designated as KIN compounds, and investigated their **antiangiogenic** activities under normoxia using a **chick** embryo **chorioallantoic** membrane. KIN-841 (2-nitroimidazole 1-acetylhydroxamate) showed a potent **angiogenic inhibition** in a dose-dependent manner. This compound inhibited the proliferation of bovine pulmonary arterial endothelial (BPAE) cells more strongly than that of tumour cells, such as Lewis lung carcinoma (3LL) cells, under normoxia. The inhibition of cell proliferation by KIN-841 under hypoxia increased about five-fold compared to that under normoxia. Moreover, under hypoxia, KIN-841 significantly decreased the excessive production of vascular endothelial cell growth factors induced by 3LL cells as determined by tritium-labelled thymidine ([(3)H]thymidine) incorporation into BPAE cells and by ELISA. Intraperitoneal **administration** of KIN-841 suppressed 3LL-cell-induced in vivo angiogenesis in the mouse dorsal air sac system. These results indicate that the regulation of the production of angiogenic factors by hypoxic tumour cells is a useful target for **tumour**-specific **angiogenesis** **inhibition**, and that KIN-841, which causes simultaneous direct inhibition of endothelial cell function and production of angiogenic factors by hypoxic **tumour** cells, is a very potent **inhibitor** of **tumour**-specific **angiogenesis**. Thus, the potential for clinical use of KIN-841 as an **antitumour** drug is very high.

L9 ANSWER 8 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003170625 EMBASE
TITLE: Potential new therapeutics for Waldenstrom's macroglobulinemia.
AUTHOR: Zeldis J.B.; Schafer P.H.; Bennett B.L.; Mercurio F.; Stirling D.I.
CORPORATE SOURCE: Dr. J.B. Zeldis, Celgene Corp., 7 Powder Horn Dr, Warren, NJ 07059, United States
SOURCE: Seminars in Oncology, (2003) 30/2 (275-281).
Refs: 25
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles

Searcher : Shears 571-272-2528

LANGUAGE: English
SUMMARY LANGUAGE: English
AB Thalidomide, the first commercially available immune modulatory drug (IMiD), has activity in the treatment of Waldenstrom's macroglobulinemia (WM), as well as multiple myeloma, myelodysplastic syndrome, myelofibrosis with myeloid metaplasia, chronic lymphocytic leukemia (CLL), and B-cell lymphomas. Although its molecular mechanisms of action have not yet been elucidated, thalidomide and the IMiDs affect a variety of cytokines and inflammatory mediators including tumor necrosis factor-alpha (TNFα), interleukin (IL)-β interferon gamma (IFNγ), IL-6, IL-10, IL-12, and COX-2 and angiogenesis factors such as **vascular endothelial growth** factor (**VEGF**) and its receptor. The IMiDs also affect adhesion molecules such as ICAM-1, ICAM-2, and L-**CAM**, in addition to preferentially stimulating CD8 cells and expanding natural killer (NK) cell populations. Since most IMiDs share these properties, it would be expected that the second-generation IMiDs (REVIMID, ACTIMID) would have activity similar to thalidomide in WM with an improved safety profile. TNFα and angiogenesis most likely play a role in promoting the growth and development of WM. The selective cytokine inhibitory drugs (SelCIDs) are potent phosphodiesterase 4 (PDE-4) inhibitors that inhibit TNFα production and are highly **antiangiogenic**. In addition, inhibition of PDE-4 induces apoptosis in human CLL lymphocytes. It is therefore expected that the SelCIDs might have activity in Waldenstrom's tumors. Jun N-terminal kinase (JNK) is a component of signaling cascades that modulate apoptosis, the induction of an inflammatory response via the AP-1 pathway, and modulation of cellular proliferation. In a variety of tumors, including multiple myeloma, JNK is induced as part of a protective mechanism. It is hypothesized that inhibition of JNK activity might allow other chemotherapeutic agents to be more effective in a similar manner to corticosteroids. Work is in progress to evaluate this. Inhibitors of the E3 subunit of ubiquitin ligase may also selectively modulate the expression of receptors, growth factors, and transcription factors essential to the growth, survival, and spread of tumors. We hypothesize that the IMiDs, SelCIDs, JNK inhibitors, and ligase inhibitors will be the basis for a new nonchemotherapeutic approach to the treatment of WM and other related diseases.

L9 ANSWER 9 OF 37 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 1030792541 JICST-EPlus
TITLE: Taxol **Inhibits** Melanoma **Metastases** Through Apoptosis Induction, **Angiogenesis Inhibition**, and Restoration of E-Cadherin and nm23 Expression
AUTHOR: WANG F; CAO Y; ZHAO W; LIU H; FU Z; HAN R
CORPORATE SOURCE: Peking Union Medical Coll., Beijing, Chn
SOURCE: J Pharmacol Sci, (2003) vol. 93, no. 2, pp. 197-203. Journal Code: G0813A (Fig. 5, Tbl. 1, Ref. 28) ISSN: 1347-8613
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
STATUS: New
AB An in vivo melanoma spontaneous metastases model was adopted to study the molecular mechanisms of the anti-metastatic effect of

Taxol. The morphology of melanoma cells in the melanoma tissue lesions was examined by hematoxylin/eosin (H&E) staining and electron microscopy. The in situ programmed cell death was tested by TUNEL analysis. **Vascular endothelial growth** factor (**VEGF**) and E-cadherin expression were detected by immunohistochemistry. The metastases suppressor gene nm23 mRNA expression level was analyzed by in situ hybridization. The results showed that i.p. injection of Taxol at 5 mg/kg per day for three weeks significantly **inhibited metastases** formation in the pulmonary of mice. Taxol induced melanogenesis and apoptosis in the melanoma cells, **inhibited angiogenesis** in melanoma tissue lesions, and reduced the expression of **VEGF**. Conversely, Taxol increased the expression of E-cadherin and nm23. In conclusion, **administration** of Taxol in the early stage of melanoma **metastases** can significantly **inhibit** melanoma **metastases**. This effect was possibly related to apoptosis induction, **tumor angiogenesis inhibition**, and restoration of the **metastasis** suppression ability. (author abst.)

L9 ANSWER 10 OF 37 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2003271997 MEDLINE
DOCUMENT NUMBER: 22683159 PubMed ID: 12799192
TITLE: Interaction of **plasminogen**-related **protein** B with endothelial and smooth muscle cells in vitro.
AUTHOR: Morioka Hideo; Morii Takeshi; Vogel Tikva; Hornicek Francis J; Weissbach Lawrence
CORPORATE SOURCE: Orthopaedic Research Laboratories, Massachusetts General Hospital and Harvard Medical School, GRJ 1124, 55 Fruit Street, Boston, MA 02114, USA.
SOURCE: EXPERIMENTAL CELL RESEARCH, (2003 Jul 1) 287 (1) 166-77.
Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030612
Last Updated on STN: 20030801
Entered Medline: 20030731

AB **Plasminogen**-related **protein** B (PRP-B) closely resembles the N-terminal **plasminogen** activation **peptide**, which is released from **plasminogen** during conversion to plasmin. We have previously demonstrated that the steady-state level of mRNA encoding PRP-B is increased within tumor tissues, and that recombinant PRP-B antagonizes neoplastic growth when **administered** systemically to mice harboring tumors, but no insights into the cell targets of PRP-B have been presented. Employing serum-free medium optimized for culturing human endothelial or smooth muscle cells, we show that recombinant PRP-B inhibits basic fibroblast growth factor-dependent cell migration for both cell types, as well as tube formation of endothelial cells. Comparison with the **angiogenesis inhibitors** angiostatin and **endostatin** revealed similar results. Recombinant PRP-B is effective in promoting cell attachment of

endothelial and smooth muscle cells, and antibody interference experiments reveal that the interaction of recombinant PRP-B with endothelial cells is mediated at least in part by alpha(v)-containing integrins. **Inhibition** of **angiogenesis** in vivo by PRP-B was demonstrated in the **chicken chorioallantoic** membrane assay. PRP-B and other **antiangiogenic** molecules may elicit metabolic perturbations in endothelial cells as well as perivascular mesenchymal cells such as smooth muscle cells and pericytes.

L9 ANSWER 11 OF 37 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2003:582949 BIOSIS
DOCUMENT NUMBER: PREV200300572771
TITLE: EFFECTS OF CYCLOOXYGENASE-2 ON ANGIOGENESIS IN PANCREATIC CARCINOMA .
AUTHOR(S): Wang, Xing-Peng [Reprint Author]; Xie, Chuan-Gao [Reprint Author]
CORPORATE SOURCE: 200080, China
SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. M2221. e-file.
Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 2003
Last Updated on STN: 10 Dec 2003

AB Objectives To investigate the effects of cyclooxygenase-2 (COX-2) on angiogenesis in pancreatic carcinoma, and to clarify the mechanisms of selective COX-2 **inhibitor** on the chemoprevention of pancreatic **carcinoma**. Methods The inhibitory effects of Celebrex, a selective cyclooxygenase-2 inhibitor, on the expression of **vascular endothelial growth** factor (**VEGF**) and PGE2 in pancreatic carcinoma cell lines PC-3 were studied by using reverse transcription polymerase chain reaction (RT-PCR), enzyme-linked immuno-adsordent assay (ELISA) and radioimmunoassay (RIA), respectively. Effects of Celebrex on the expression of **VEGF** and PGE2 in pancreatic tumor of xenografted nude mice induced by PC-3 cell lines were investigated by immunohistochemistry, RT-PCR and Western blot. Microvessel density (MVD) was also determined under microscope. The COX-2 antisense oligdeoxynucletids (ODNs) was designed, synthesized, and transfected into PC-3 cell lines. The transfection effects were confirmed by fluorescence microscope, RT-PCR and Western blot. Chorioallantoic membrane (**CAM**) grafted model was used to evaluate the effects of COX-2 anti-ODNs and PGE2 on the angiogenesis in pancreatic carcinoma. Results The expression of **VEGF** and PGE2 was inhibited by Celebrex in a certain degree with time-dependent and dose-dependent manner. Celebrex could inhibit the expression of **VEGF** and PGE2 in the xenografted tumor of PC-3 cell lines in nude mice, and also could decrease the average MVD significantly in tumor tissue ($P<0.05$). The expression of COX-2

mRNA and **protein** was decreased after transfecting COX-2 anti-ODNs in PC-3 cell lines. **Administration** of COX-2 anti-ODNs resulted in the suppression of angiogenesis in PC-3 cell **CAM** xenografted model, while this inhibitory effect can be reversed partially by exogenous PGE2. Conclusions COX-2 may play an important role in the angiogenesis of pancreatic carcinoma, while PGE2 is likely to act as an important intermediate part in this process. The results suggest that the inhibition of COX-2 may be used to **treat** pancreatic **carcinoma** by **inhibition** of **angiogenesis**..

L9 ANSWER 12 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-201312 [19] WPIDS
DOC. NO. CPI: C2003-051152
TITLE: Photosensitizer immunoconjugate composition useful for **treating cancer** comprises at least one photosensitizer and at least one solubilizing agent.
DERWENT CLASS: B05 D16 P34
INVENTOR(S): HASAN, T; SAVELLANO, M D; SKOBE, M
PATENT ASSIGNEE(S): (HASA-I) HASAN T; (SAVE-I) SAVELLANO M D; (SKOB-I) SKOBE M; (GEHO) GEN HOSPITAL CORP
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002100326	A2	20021219	(200319)*	EN	62
US 2002197262	A1	20021226	(200319)		

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002100326	A2	WO 2002-US13776	20020501
US 2002197262	A1 Provisional	US 2001-287767P	20010501
	Provisional	US 2001-338961P	20011207
		US 2002-137029	20020501

PRIORITY APPLN. INFO: US 2001-338961P 20011207; US 2001-287767P 20010501; US 2002-137029 20020501
AN 2003-201312 [19] WPIDS
AB WO2002100326 A UPAB: 20030320
NOVELTY - A purified photosensitizer immunoconjugate (PIC1) composition comprises at least one photosensitizer (p1) and at least one solubilizing agent, each independently bound to an antibody through a direct covalent linkage.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) The photosensitizer immunoconjugate (PIC2) composition

comprising a number of (p1) covalently linked to an antibody at a density to quench photoactivation while the composition is freely circulating throughout the bloodstream;

(2) Detection of tumor cell involving **administration** of the composition, localizing the composition to the tumor cell, light-activating the composition to illuminate the tumor cell;

(3) Reduction (R1) of tumor cell growth and/or proliferation involving **administration** of PIC composition, localizing the composition to the tumor cell, light-activating the composition to produce phototoxic species;

(4) Preparation of the compositions involving:

(a) preparing PEGylated antibodies by conjugating antibodies with PEG-NHS esters in which 4 or fewer lysine residues per antibody are PEGylated; and

(b) conjugating the PEGylated antibodies to a purified, activated photosensitizer-NHS esters to form PIC involving antibodies and photosensitizers having less than twenty amide linkages between unPEGylated lysine residues of each antibody and the photosensitizers.

ACTIVITY - Cytostatic; **Antitumor**.

MECHANISM OF ACTION - **Tumor** cell growth **inhibitor**.

Mice injected with **tumor** cell injection were **treated** with a composition (test) comprising BPD and IMC-C225. As a control no treatment was given to some mice. The weight loss (g) after 21 days for test/control was found to be 2.09/2.66.

USE - In the **treatment** of **tumor** (claimed). Also useful for the **treatment** of **cancer**, including ovarian **cancer**. For **treating** and imaging brain **cancer**.

ADVANTAGE - The compositions are of high purity and are thus ideal for diagnostic applications requiring a high degree of specificity. Combination therapies, as well as selective photodynamic therapies and diagnostic methods can now utilize improved PICs.

Dwg.0/20

L9 ANSWER 13 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2003-018859 [01] WPIDS

DOC. NO. CPI: C2003-004629

TITLE: Use of a pure histidine-rich glycoprotein **polypeptide** as an anti-**neoplastic** agent in the **treatment** of e.g. **cancer**.

DERWENT CLASS: B04 B05 D16

INVENTOR(S): CLAESSON-WELSH, L; LARSSON, H; OLSSON, A; WELSH, L C

PATENT ASSIGNEE(S): (CLAE-I) CLAESSON-WELSH L; (LARS-I) LARSSON H; (OLSS-I) OLSSON A; (INNO-N) INNOVENTUS PROJECT AB

COUNTRY COUNT: 101

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002076486	A2	20021003	(200301)*	EN	49

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ
DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP
KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ
NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ
UA UG US UZ VN YU ZA ZW

US 2002165131 A1 20021107 (200301)

EP 1357930 A2 20031105 (200377) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK
NL PT RO SE SI TR

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002076486	A2	WO 2002-IB2425	20020204
US 2002165131	A1 Provisional	US 2001-266505P	20010205
		US 2002-67093	20020204
EP 1357930	A2	EP 2002-733167	20020204
		WO 2002-IB2425	20020204

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1357930	A2 Based on	WO 2002076486

PRIORITY APPLN. INFO: US 2001-266505P 20010205; US 2002-67093 20020204

AN 2003-018859 [01] WPIDS

AB WO 200276486 A UPAB: 20030101

NOVELTY - Use of a pure histidine-rich glycoprotein **polypeptide** (HRGP) (A) as an anti-angiogenic agent, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(1) a composition comprising (A);

(2) an article of manufacture comprising packaging material and (A) within the packaging material. The packaging material comprises a label or package insert indicating that (A) is to be **administered** to a mammal for the **inhibition** of **angiogenesis**;

(3) identifying (A) involving:

(a) measuring the effect of (A) either upon growth of the angiogenesis-dependent tumor, or upon fibroblast growth factor 2 (FGF-2), or upon **chick chorioallantoic** membrane angiogenesis; and

(b) identifying (A) as an anti-angiogenic **polypeptide** when either the tumor growth is decreased, or FGF-2 induced migration is decreased, or **chick chorioallantoic** membrane is decreased respectively in the presence of the (A);

(4) an antibody that binds to (A);

(5) **inhibiting angiogenesis** in a mammal by **administering** (A) or an antibody, which is agonistic for angiogenesis;

(6) stimulating angiogenesis in a mammal by **administering** an antibody, which is antagonistic for angiogenesis;

(7) imaging neovascularization in a mammal by **administering** (A) coupled to a detectable marker to the mammal, and measuring neovascularization in the mammal based on the

detectable marker;
(8) (A) coupled to a detectable marker or toxin;
(9) a receptor that binds to (A);
(10) plasma (preferably human plasma) depleted of (A);
(11) an isolated polynucleotide encoding (A);
(12) a vector comprising the polynucleotide; and
(13) a host cell comprising the vector.
ACTIVITY - Cytostatic; Antidiabetic; Ophthalmological; Antiinflammatory; Antipsoriatic.
MECHANISM OF ACTION - **Angiogenesis inhibitor**; Chorioallantoic membrane (**CAM**) **angiogenesis**; Endothelial cell migration **inhibitor**; **tumor** growth **inhibitor**.
Histidine-rich glycoprotein **polypeptide** (HRGP) inhibited growth of fibrosarcoma in mice was studied. HRGP purified from human plasma was used to treat C57/black mice, carrying palpable, subcutaneous T241 fibrosarcomas on the left flank. As a control, C57/b;ack mice were treated with phosphate buffered saline (PBS). Treatments were given daily, as subcutaneous injections at a dose of 4 mg/kg in the right flank, until the size of control tumor reached the upper level of 2.5 cm2.
It was observed that the injections with HRGP led to a drastic reduction in tumor growth. At the time of sacrifice, the size of tumors was reduced by about 75%. In parallel, **tumor**-bearing animals were **treated** with thermolysin cleaved antithrombin. There was no statistically significant difference in **tumor** size between PBS-**treated** animals and animals treated with thermolysin cleaved antithrombin. The results indicated that the effect of HRGP was not due to manipulations or injection of **protein**, in general, and HRGP had anti-angiogenic activity as measured by fibrosarcoma tumor growth assay.
USE - The composition is used for:
(a) **inhibiting angiogenesis** in a mammal (such as a mouse, rat or human), e.g. cancer, a condition such as myocardial angiogenesis, diabetic retinopathy, diabetic neovascularization, inappropriate wound healing and antiinflammatory disease;
(b) for birth control in a female mammal (claimed);
(c) to immunize animals;
(d) for **treating** several **angiogenic**-dependent **cancers** such as rhabdomyosarcoma, glioblastoma, multiform, bladder carcinoma, pancreatic carcinoma, renal carcinoma, leiomyosarcoma, prostate carcinoma, mammary carcinoma, lung carcinoma, and other angiogenic diseases such as retrolental fibroplasias, trachoma, neovascular glaucoma, psoriasis, angio-fibromas, immune and non-immune inflammation, capillary formation within atherosclerotic plaques, myocardial angiogenesis, hemangiomas, excessive wound repair, various inflammatory diseases and any disease condition involving excessive and/or deregulated angiogenesis.
ADVANTAGE - (A) **inhibits** chorioallantoic membrane (**CAM**) **angiogenesis**, endothelial cell migration and tumor growth.
Dwg.0/4

L9 ANSWER 14 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-490049 [52] WPIDS
DOC. NO. CPI: C2002-139131

TITLE: Treating a neuronal deficiency, particularly epilepsy, senile dementia or schizophrenia, by **administering** bone marrow-derived cells to an individual to induce the formation of new neurons in the nervous system.

DERWENT CLASS: B04 D16

INVENTOR(S): BLAU, H M; BRAZELTON, T R

PATENT ASSIGNEE(S): (STRD) UNIV LELAND STANFORD JUNIOR; (BLAU-I) BLAU H M; (BRAZ-I) BRAZELTON T R

COUNTRY COUNT: 23

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002037968	A1	20020516	(200252)*	EN	46
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR					
W: AU CA JP					
AU 2002019830	A	20020521	(200260)		
US 2002168350	A1	20021114	(200277)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002037968	A1	WO 2001-US43806	20011113
AU 2002019830	A	AU 2002-19830	20011113
US 2002168350	A1 Provisional	US 2000-247128P	20001110
		US 2001-993045	20011113

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002019830	A Based on	WO 2002037968

PRIORITY APPLN. INFO: US 2000-247128P 20001110; US 2001-993045 20011113

AN 2002-490049 [52] WPIDS

AB WO 200237968 A UPAB: 20020815

NOVELTY - Treating a neuronal deficiency, comprises **administering** bone marrow-derived cells to an individual having neuronal deficiency to induce the formation of new neurons in a nervous system of the subject, is new.

DETAILED DESCRIPTION - Treating a neuronal deficiency, comprises:

(a) **administering** bone marrow-derived cells to an individual having a neuronal deficiency to induce the formation of new neurons in the nervous system of the subject; and

(b) ameliorating at least one symptom of the neuronal deficiency.

ACTIVITY - Neuroprotective; nootropic; anticonvulsant; tranquilizer; vulnerary; vasotropic; neuroleptic; cytostatic.

No biological data given.

MECHANISM OF ACTION - Bone marrow cell mobilization therapy; neuron formation inducer.

USE - The method is useful for treating a neuronal deficiency, particularly those that do not arise from any of the disorders a lysosomal or peroxisomal disorder, Zellweger's disease, human

immunodeficiency virus (HIV) infection, multiple sclerosis, adrenoleucodystrophy, adrenomyeloneuropathy, a metachromatic leucodystrophy, a sulphatide lipidosis, globoid cell leucodystrophy, amyotrophic lateral sclerosis, amyotrophic lateral sclerosis with frontal lobe dementia, a bone marrow ablation **treatment**, lymphoreticular, disorders, **metastases** of **tumors** that do not arise in the nervous system, infantile acid maltase deficiency (Pompe's disease), Ceroid lipofuscinosis, a deficiency of GM2 gangliosidase, Sanfilippo's disease, leucodystrophy, systemic lupus erythematosus, thrombophilia associated with antiphospholipid antibodies or polycythemia, or anemia (e.g. Sickle cell disease, beta-Thalassemia major or other thalassemias), in a subject (specifically a human).

The method is particularly useful for treating neuronal deficiencies that arise from abnormalities of the central autonomic systems, congenital disorders and disorders arising from teratogen exposure, demyelinating diseases, diseases of peripheral nerves, disorders of the hypothalamus and pituitary, disorders of movement, disorders of the spinal cord and vertebral column, epilepsy, hypoxia, increased intracranial pressure, infectious disease, neoplasia, neurodegenerative disorders, neuronal disorders associated with aging and senile dementia, nutritional disorders, perinatal neuropathologies, radiation damage, schizophrenia, single gene disorders, toxic disorders, trauma, vascular disease, or psychiatric disorders other than schizophrenia.

The method is also useful for improving memory function in an ind ividual with deficient memory function.

Dwg.0/0

L9 ANSWER 15 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-416623 [44] WPIDS
DOC. NO. CPI: C2002-117517
TITLE: Enhancing **angiogenesis** to **treat** diseases associated with deficient **angiogenesis**, such as wound healing disorders, comprises **administering** an integrin binding pro-angiogenic agent, e.g., neural cell adhesion molecule L1.
DERWENT CLASS: B04 D16
INVENTOR(S): BROOKS, P; MONTGOMERY, A; REISFELD, R A
PATENT ASSIGNEE(S): (SCRI) SCRIPPS RES INST
COUNTRY COUNT: 98
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002028355	A2	20020411	(200244)*	EN	42
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2002011824	A	20020415	(200254)		
EP 1363653	A2	20031126	(200380)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002028355	A2	WO 2001-US42375	20010926
AU 2002011824	A	AU 2002-11824	20010926
EP 1363653	A2	EP 2001-979907	20010926
		WO 2001-US42375	20010926

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2002011824	A	Based on	WO 2002028355
EP 1363653	A2	Based on	WO 2002028355

PRIORITY APPLN. INFO: US 2000-237739P 20001002
AN 2002-416623 [44] WPIDS
AB WO 200228355 A UPAB: 20020711
NOVELTY - Enhancing angiogenesis (M1), comprises **administering** an integrin binding pro-angiogenic agent to a mammal, where angiogenesis is desirable, to enhance angiogenesis in the mammal, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated **protein** or **peptide** consisting of the entire extracellular domain of the NCAM L1 or a functional derivative or fragment that substantially retains its binding affinity with the integrin, a NCAM L1 comprising the Ig-like domains 4-6 (Ig 4-6) or a functional derivative or fragment that substantially retains its binding affinity with the integrin, a **protein** or a **peptide** that specifically binds to an antibody that is raised against a **peptide** or a **peptide** having the fully defined **amino** sequence S1 given in specification;

(2) a pharmaceutical composition (I) comprising an isolated **protein** or **peptide** and a pharmaceutically acceptable carrier or excipient;

(3) an isolated nucleic acid encoding a **protein** or **peptide** consisting of the entire extracellular domain of the NCAM L1 or a functional derivative or fragment that substantially retains its binding affinity with the integrin, a NCAM L1 comprising the Ig-like domains 4-6 (Ig 4-6) or a functional derivative or fragment that substantially retains its binding affinity with the integrin, a **protein** or a **peptide** that specifically binds to an antibody that is raised against a **peptide** having the **amino** sequences S1 or S2;

(4) a pharmaceutical composition (II) comprising a nucleic acid and a pharmaceutically acceptable carrier or excipient;

(5) a combination (C1) comprising an integrin binding pro-angiogenic agent and another angiogenic molecule;

(6) enhancing (M2) angiogenesis comprising **administering** C1 to a mammal where angiogenesis is desirable, to enhance angiogenesis in a mammal;

(7) enhancing (M3) angiogenesis comprising **administering** an integrin antagonist to a mammal where the angiogenesis is desirable, to enhance angiogenesis; and

(8) a combination (C2) comprising an integrin antagonist and another angiogenic molecule.

ACTIVITY - Vasotropic; vulnerary; angiogenic.

No supporting data.

MECHANISM OF ACTION - Angiogenesis-Stimulator.

To determine whether soluble L1 **polypeptides** can induce angiogenesis, 3 L1 GST fusion **proteins** that together span the entire extracellular domain of L1. The fusion **proteins** consists of Ig-like domains 1-3 and 4-6 and fibronectin like domains FN 1-5. The ability of these fusion **proteins** to induce angiogensis was assessed in the **chick chorioallantoic** model. Results showed that the induction of a significant angiogenic response was produced by the fragment containing Ig-like domains 4 to 6. Such a response was not observed in equimolar amounts of the fibronectin-like domains of L1 (FN-1-5), and immunoglobulins 1-3 induced only a limited response. The response induced by Ig 4-6 was comparable to that induced by bFGF used at a concentration optimal for the induction of an angiogenic response.

USE - M1 is used to enhance angiogenesis in a mammal, such as a human (claimed), to treat disorders or diseases associated with deficient angiogenesis, such as ischemic diseases or wound healing disorders, by **administering** an integrin binding pro-angiogenic agent to the mammal.

Dwg.0/4

L9 ANSWER 16 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-405017 [43] WPIDS
DOC. NO. CPI: C2002-113753
TITLE: Treatment of e.g. Alzheimer's disease comprises external application of pulses to fluid channels in patients' body.
DERWENT CLASS: B04 B05 D16
INVENTOR(S): INMAN, D M; SACKNER, M A
PATENT ASSIGNEE(S): (NONI-N) NON-INVASIVE MONITORING SYSTEMS INC
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002026194	A2	20020404	(200243)*	EN	207

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2002012996 A 20020408 (200252)
US 2002103454 A1 20020801 (200253)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002026194	A2	WO 2001-US30789	20010928
AU 2002012996	A	AU 2002-12996	20010928
US 2002103454	A1 Provisional	US 2000-236221P	20000928

US 2001-967422 20010928

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002012996 A	Based on	WO 2002026194

PRIORITY APPLN. INFO: US 2000-236221P 20000928; US 2001-967422 20010928

AN 2002-405017 [43] WPIDS

AB WO 200226194 A UPAB: 20020709

NOVELTY - Treating (I) e.g. Alzheimer's disease comprising the external application of pulses to the fluid channels in the patients' body, is new.

DETAILED DESCRIPTION - Treatment of e.g. Alzheimer's disease comprises:

(a) periodically accelerating at least one part of the body using a periodic acceleration device, externally and non-invasively apply a pulse to the fluid channels (A1) over the body's own pulse (A2); and

(b) stimulating endothelial release of beneficial mediators and suppressing non-beneficial mediators. The pulses are not synchronized with (A2).

An INDEPENDENT CLAIM is included for diagnosing (II) a subject involving steps (a) and (b) and testing the physiological response of the subject either during or immediately after step (b) using the device.

ACTIVITY - Nootropic; Neuroprotective; Cerebroprotective; Hemostatic; Antiparkinson; Anticonvulsant; Antiinflammatory; Vasotropic; Antibacterial; Immunosuppressive; Cardiant; Thrombolytic; Osteopathic; Antianginal; Antiarteriosclerotic; Hypotensive; Opthalmological; Antidiabetic; Anorectic; Tranquilizer; Vulnerary; Antidepressant; Analgesic; Auditory; Antirheumatic; Antiarthritic; Anti-HIV; Cytostatic; **Antitumor**.

MECHANISM OF ACTION - Inhibitor; Promoter; Stimulator.

USE - The method is useful for treating depression, chronic fatigue syndrome, panic, anxiety, schizophrenia, conversion and somatoform pain disorder, alcohol abuse and dependence, Alzheimer's disease, acute brain injury, chronic neurogenerative disease, inflammation, heart disorders, impaired lymphatic drainage, for promoting bone growth where mediator release is deficient, for providing cerebrospinal fluid drainage, vasodilation and increased blood flow, chronic heart failure, acute myocardial infarction, vasopathic angina, coronary atherosclerosis and asymptomatic coronary artery disease, diastolic dysfunction, systemic, portal, obesity related and pulmonary hypertension, Raynauld's phenomenon, proliferative retinopathy, insulin resistance syndrome, wide-angle glaucoma, macular degeneration, angina pectoris, restenosis, vasospastic angina, for preparing the myocardium for redo coronary bypass graft surgery and graft failure, type-2 diabetes mellitus, preconditioning the heart to minimize reperfusion injury, myocardial ischemia, renal failure complicated by arterial stiffness, chronic atrial fibrillation, ischemic stroke, subarachnoid hemorrhage, for a neonatal patient with neonatal pulmonary hypertension caused by genetic deficiency of endothelial nitric oxide synthase (eNOS), bronchopulmonary dysplasia, pulmonary embolism, venous stasis, endothelial dysfunction, dysmenorrhea, preeclampsia, preterm

cervical dilitation, traumatic brain injury, pain management, sleep deprivation, sudden deafness and Menier's disease, lymphatic damage, adult respiratory distress syndrome and meconium aspiration syndrome, osteoporosis, bone fractures, fibromyalgia, wounds, bed sores, tendon damage, acute gastric injury, HIV-1 infection, erectile dysfunction, cancer, prostate cancer with an overexpression of endothelin-1 and for the improvement of memory and cognitive function. Method (II) is useful for diagnosing atherosclerosis, hypercholesterolemia, insulin resistance syndrome, arterial smooth muscle dysfunction, microvascular cerebrovascular disorders and normal pressure glaucoma, diabetes and chronic heart failure (all claimed).

ADVANTAGE - The method stimulates the endothelial release of beneficial mediator and suppresses non-beneficial mediators so the pulses do not encroach on the patient pulse wave. Advantages also include e.g. endothelial release of nitric oxide, prostacyclin and tissue **plasminogen** activator and suppression of endothelin-1, tissue **plasminogen** inhibitor and antigen helps prevent graft rejection. For vasopathic angina (I) upregulates coronary vascular eNOS to release nitric oxide thus diminishing the frequency and intensity of coronary spasm episodes. During treatment of hepatic veno-occlusive disease (I) upregulates endothelial storage and release of tissue plasmingen activator and suppresses tissue **plasminogen** inhibitor. The externally added pulses improve memory and cognitive function.

Dwg.0/0

L9 ANSWER 17 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002442330 EMBASE

TITLE: Domain swapping in a COOH-terminal fragment of platelet factor 4 generates potent **angiogenesis inhibitors.**

AUTHOR: Hagedorn M.; Zilberberg L.; Wilting J.; Canron X.; Carrabba G.; Giussani C.; Pluderi M.; Bello L.; Bikfalvi A.

CORPORATE SOURCE: A. Bikfalvi, Inst. Natl. Sante/Rech. Medicale, EMI 0113 Molec. Mech. Angiogenesis, Universite Bordeaux 1, Avenue des Facultes, 33 405 Talence, France. a.bikfalvi@croissance.u-bordeaux.fr

SOURCE: Cancer Research, (1 Dec 2002) 62/23 (6884-6890). Refs: 58
ISSN: 0008-5472 CODEN: CNREA8

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB A few **peptide** residues in structurally important locations often determine biological functions of **proteins** implicated in the regulation of angiogenesis. We have shown recently that the short COOH-terminal segment PF-4(47-70) derived from platelet factor 4 (PF-4) is the smallest sequence that conserves potent **antiangiogenic** activity in vitro and in vivo. Here we show that modified COOH-terminal PF-4 **peptides**

containing the sequence ELR (or related DLR), a critical domain present in proangiogenic chemokines, surprisingly elicit several times greater **antiangiogenic** potential than the original **peptide.** The modified **peptides** inhibit binding of iodinated **vascular endothelial growth** factor and fibroblast growth factor 2 to endothelial cell receptors, endothelial cell proliferation, migration, and microvessel assembly in the rat aortic ring model at lower doses than PF-4(47-70). On the differentiated **chick chorioallantoic** membrane, topical application of 40 μg of modified **peptides** potently reduces capillary angiogenesis induced by **vascular endothelial growth** factor (165), a dose where **peptide** PF-4(47-70) was inactive. Established intracranial glioma in nude mice decreased significantly in size when treated locally with a total dose of 250 μg of **peptide** PF-4(47-70) DLR (n = 10) compared with the same dose of the original PF-44(7-70) **peptide** (n = 10) or controls (n = 30). Tailored PF-4 **peptides** represent a new class of **antiangiogenic** agents with a defined mode of action and a strong in vivo activity.

L9 ANSWER 18 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2002:757994 SCISEARCH
THE GENUINE ARTICLE: 590ZC
TITLE: A gene **therapy** for **cancer** based on the **angiogenesis inhibitor,** vasostatin
AUTHOR: Xiao F; Wei Y (Reprint); Yang L; Zhao X; Tian L; Ding Z; Yuan S; Lou Y; Liu F; Wen Y; Li J; Deng H; Kang B; Mao Y; Lei S; He Q; Su J; Lu Y; Niu T; Hou J; Huang M J
CORPORATE SOURCE: Sichuan Univ, W China Hosp, W China Med Sch, Key Lab Biotherapy Human Dis, Guo Xue Xiang, 37, Chengdu 610041, Peoples R China (Reprint); Sichuan Univ, W China Hosp, W China Med Sch, Key Lab Biotherapy Human Dis, Chengdu 610041, Peoples R China; Sichuan Univ, W China Hosp, W China Med Sch, Ctr Canc, Chengdu 610041, Peoples R China; Sichuan Univ, Univ Hosp 2, W China Med Sch, Dept Gynecol & Obstet, Sichuan, Peoples R China
COUNTRY OF AUTHOR: Peoples R China
SOURCE: GENE THERAPY, (SEP 2002) Vol. 9, No. 18, pp. 1207-1213.
Publisher: NATURE PUBLISHING GROUP, MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND.
ISSN: 0969-7128.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 44
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The growth and persistence of solid tumors and their metastasis are angiogenesis-dependent. Vasostatin, the N-terminal domain of calreticulin inclusive of **amino** acids 1-180, is a potent **angiogenesis inhibitor.** To investigate whether intramuscular **administration** of vasostatin gene has the **antitumor** activity in mouse tumor models, we constructed a plasmid DNA encoding vasostatin and a control vector. Production and secretion of vasostatin **protein** by COS cells transfected

with the plasmid DNA encoding vasostatin (pSecTag2B-vaso) were confirmed by Western blot analysis and ELISA. Conditioned medium from vasostatin-transfected COS cells apparently inhibited human umbilical vein endothelial cell (HUVEC) and mouse endothelial cell (SVEC4-10) proliferation, compared with conditioned medium from the COS cells transfected with control vector or non-transfected cells. Treatment with pSecTag2B-vaso twice weekly for 4 weeks resulted in the **inhibition** of **tumor** growth and the prolongation of the survival of tumor-bearing mice. The sustained high level of vasostatin **protein** in serum could be identified in ELISA. **Angiogenesis** was apparently **inhibited** in **tumor** by immunohistochemical analysis. **Angiogenesis** was also **inhibited** in the chicken embryo **CAM** assay and mouse corneal micropocket assay. The increased apoptotic cells were found within the **tumor** tissues from the mice **treated** with plasmid DNA encoding vasostatin. Taken together, the data in the present study indicate that the **cancer** gene **therapy** by the intramuscular delivery of plasmid DNA encoding vasostatin, is effective in the **inhibition** of the systemic **angiogenesis** and **tumor** growth in murine models. The present findings also provide further evidence of the anti-tumor effects of the vasostatin, and may be of importance for the further exploration of the application of this molecule in the **treatment** of **cancer**.

L9 ANSWER 19 OF 37 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 2002299753 MEDLINE
DOCUMENT NUMBER: 21984594 PubMed ID: 11988857
TITLE: Angiogenic activity of beta-sitosterol in the ischaemia/reperfusion-damaged brain of Mongolian gerbil.
AUTHOR: Choi Seongwon; Kim Kyu-Won; Choi Jae-Sue; Han Sang-Taek; Park Young-In; Lee Seung-Ki; Kim Jeong-Soon; Chung Myung-Hee
CORPORATE SOURCE: Department of Pharmacology, Seoul National University College of Medicine, Seoul, Korea.
SOURCE: PLANTA MEDICA, (2002 Apr) 68 (4) 330-5. Journal code: 0066751. ISSN: 0032-0943.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020604
Last Updated on STN: 20020716
Entered Medline: 20020715

AB Aloe vera continues to be used for wound healing as a folk medicine. We previously reported that A. vera gel has angiogenic activity. In this study, we report upon the isolation of an angiogenic component beta-sitosterol from A. vera and examination of its effect upon damaged blood vessels of the Mongolian gerbil. In a **chick** embryo **chorioallantoic** membrane assay, beta-sitosterol was found to have an angiogenic effect. It enhanced new vessel formation in gerbil brains damaged by ischaemia/reperfusion, especially in the cingulated cortex and septal regions, in a dose-dependent fashion (up to 500 microg/kg, $p < 0.05$, $n = 34 - 40$). beta-Sitosterol also enhanced the expressions of **proteins**

related to angiogenesis, namely von Willebrand factors, **vascular endothelial growth** factor (**VEGF**), **VEGF** receptor Flk-1, and blood vessel matrix laminin ($p < 0.05$, $n = 6$). In addition, the intraperitoneal **administration** of beta-sitosterol at 500 microg/kg/day for a period of 19 days significantly improved the motion recovery of ischaemia/reperfusion-damaged gerbils as assessed by rota-rod testing ($p < 0.001$, $n = 10$). Our results suggest that beta-sitosterol has **therapeutic angiogenic** effects on damaged blood vessels.

L9 ANSWER 20 OF 37 MEDLINE on STN
ACCESSION NUMBER: 2002132166 MEDLINE
DOCUMENT NUMBER: 21856941 PubMed ID: 11866542
TITLE: Advanced glycation end products induce angiogenesis in vivo.
AUTHOR: Okamoto Tamami; Tanaka Shinya; Stan Alex C; Koike Takao; Kase Manabu; Makita Zenji; Sawa Hirofumi; Nagashima Kazuo
CORPORATE SOURCE: Laboratory of Molecular & Cellular Pathology, Hokkaido University School of Medicine, N 15, W7, Kita-ku, Sapporo, 060-8638, Japan.
SOURCE: MICROVASCULAR RESEARCH, (2002 Mar) 63 (2) 186-95. Journal code: 0165035. ISSN: 0026-2862.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020228
Last Updated on STN: 20020611
Entered Medline: 20020610

AB Advanced glycation end products (AGEs) have been thought to participate in diabetic microangiopathy. However, the effects of AGEs on angiogenesis have so far been mainly examined either in vitro or by using cultured cells. In the present study, we have analyzed whether AGEs induce angiogenesis in vivo by using the chorioallantoic membrane (**CAM**) assay. The **CAM** assay was carried out in embryonated hen eggs to determine the effects of AGEs. Following generation of AGEs based on bovine serum albumin (BSA), either AGE-BSA or nonglycated BSA was **administered** to the **CAM** and their effects on **angiogenesis** were assessed, together with an **inhibitory** effect of an anti-AGE antibody against AGE-BSA-induced angiogenesis. The histological features of AGE-induced vascular lumens were examined by immunohistochemical analysis for Factor VIII and smooth muscle alpha-actin. AGE-BSA induced angiogenesis in **CAM** in a dose- and time-dependent manner. AGE-induced angiogenesis on **CAM** was neutralized by the anti-AGE antibody. Immunohistochemical analysis demonstrated that AGE-induced vascular lumens were devoid of pericytes. Our data demonstrated that AGEs are an angiogenetic factor and that our system of AGE-induced abnormal vessels in **CAMs** is useful in further investigations of the mechanism of diabetic retinal angiogenesis and can also be used to provide a therapeutic model for diabetic angiopathy.

L9 ANSWER 21 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2001-626377 [72] WPIDS
CROSS REFERENCE: 2002-010784 [01]
DOC. NO. CPI: C2001-186634
TITLE: New human truncated tyrosyl-tRNA synthetase **polypeptide** for regulating vascular endothelial function, in particular for regulating **angiogenesis, tumor metastasis** and **treating** myocardial infarction.
DERWENT CLASS: B04 D16
INVENTOR(S): SCHIMMEL, P; WAKASUGI, K
PATENT ASSIGNEE(S): (SCRI) SCRIPPS RES INST
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001074841	A1	20011011	(200172)*	EN	150
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001050904	A	20011015	(200209)		
EP 1272506	A1	20030108	(200311)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
JP 2003529354	W	20031007	(200370)		158

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001074841	A1	WO 2001-US8966	20010321
AU 2001050904	A	AU 2001-50904	20010321
EP 1272506	A1	EP 2001-924232	20010321
		WO 2001-US8966	20010321
JP 2003529354	W	JP 2001-572530	20010321
		WO 2001-US8966	20010321

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001050904	A	Based on	WO 2001074841
EP 1272506	A1	Based on	WO 2001074841
JP 2003529354	W	Based on	WO 2001074841

PRIORITY APPLN. INFO: US 2000-193471P 20000331
AN 2001-626377 [72] WPIDS
CR 2002-010784 [01]
AB WO 200174841 A UPAB: 20031030
NOVELTY - An isolated **polypeptide** (I) comprising a truncated tyrosyl-tRNA synthetase **polypeptide** comprising a Rossmann fold nucleotide binding domain, capable of regulating vascular endothelial cell function, where (I) is of approx. 40 kilo

Dalton molecular weight and is produced by cleavage of the **polypeptide** having a fully defined sequence (S1) of 536 **amino** acids as given in the specification with polymorphonuclear leucocyte elastase, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated **polypeptide** (II) which is a synthetic, truncated tyrosyl-tRNA synthetase (TyrRS) **polypeptide** having chemokine activity;

(2) an isolated nucleic acid molecule (III) comprising:

(a) a polynucleotide having a nucleotide sequence 95% identical to a fully defined sequence (S2) of 5174 base pairs (bp) as given in the specification;

(b) a polynucleotide encoding (I) or a **polypeptide** epitope of (S1); or

(c) a polynucleotide hybridizable to (II) or a polynucleotide encoding (I);

(3) an isolated nucleic acid molecule (IV) that encodes (II);

(4) a recombinant vector (V) comprising (III) or (IV);

(5) a recombinant host cell (VI) that expresses (I) or (II);

(6) making a recombinant host cell by introducing (III) into the host cell;

(7) a recombinant host cell produced by the above method;

(8) an isolated antibody (VII) that specifically binds to (I) or (II);

(9) producing (I) or (II); and (10) a composition comprising (I) or (II);

(10) regulating angiogenesis or tumor metastasis comprising **administering** (I) or (II) to a mammal;

(11) enhancing or suppressing angiogenesis (to a graft) in a mammal comprising **administering** a composition containing (I) to the mammal;

(12) treating myocardial infarction in a mammal comprising **administering** a composition containing (I) to the mammal;

(13) treating a condition that would benefit from decreased or increased angiogenesis in a mammal comprising **administering** a composition containing (I);

(14) **treating** a solid **tumor** in a mammal comprising **administering** a composition containing (I); and

(15) diagnosing a (susceptibility to a) pathological condition comprising determining the presence or absence of a mutation in (III) or determining the presence or absence of expression of (I).

ACTIVITY - Cytostatic; cardiant; antiinflammatory; vulnerary; antiulcer.

MECHANISM OF ACTION - Gene **therapy**; regulator of **angiogenesis**. In vivo **angiogenesis** assays were conducted in **chick chorioallantoic** membrane (**CAM**). 10-day-old **chick** embryos were incubated at 37 deg. C and 70% humidity. A small hole was made with a small crafts drill directly over the air sac at the end of the egg. Negative pressure was applied to the original hole, which resulted in **CAM** pulling away from the shell membrane and creating a false air sac. A window was cut in the eggshell over the dropped **CAM**, exposing the **CAM** to directly access for experimental manipulation. Cortisone acetate-treated 5 mm filter disks were soaked with a **protein** sample (25 ng of **vascular endothelial growth** factor (**VEGF**)(165) or 250 ng of a TyrRS molecule) and the filter

disks were added directly to the **CAMs**. At 0, 24 and 48 hours following incubation, 3 micro g of interferon- alpha inducible **protein** was topically applied to the filter disks. After 72 hours, the **CAM** tissue associated with the filter disk was harvested and quantified using a stereomicroscope. Angiogenesis was assessed as the number of visible blood vessel branch points within the defined area of the filter disks. The results showed that the human mini TyrRS induced angiogenesis. The angiostatic activity of human full-length TrpRS and human mini-TrpRS was also analyzed in in vivo angiogenesis assays conducted in chick **CAM** with 3 micro g of full-length TrpRS or mini TrpRS added to **VEGF** (165)-induced or mini TryRS-induced **CAM** tissue. The angiogenic activity of human **VEGF**(165) and human mini TryRS was inhibited by human mini TrpRS. Human full-length TrpRS had no observable angiostatic activity.

USE - (I) is useful for regulating angiogenesis, tumor **metastasis**, enhancing **angiogenesis** to a graft, **treating** myocardial infarction, solid **tumor**, and a condition that would benefit from increased or decreased angiogenesis in a mammal, in particular humans. (I) and (III) are useful for diagnosing a pathological condition or susceptibility to a pathological condition in a subject, by determining the presence or amount of expression of (I) in a biological sample or by determining the presence or absence of a mutation in (III). (VI) is useful for producing an isolated **polypeptide**. (I) is also useful for preparing a pharmaceutical composition (claimed). (I) is useful as wound healing agent for treating wounds such as dermal ulcers, diabetic ulcers, burns and injuries and in plastic surgery when reconstruction is required following a burn or for cosmetic purposes. (I) is particularly useful in the treatment of abdominal wounds where there is high risk of infection. (I) promotes endothelialization in vascular graft surgery and is used in conjunction with angiography to **administer** the angiogenic tRNA synthetase **polypeptides** or polynucleotides directly to the lumen and wall of the blood vessel. (I) is useful as an immunogen to produce antibodies which are useful to isolate the **polypeptide** from tissue expressing the **polypeptide** and to treat inflammation caused by increased vascular permeability. Dwg.0/25

L9 ANSWER 22 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-656972 [75] WPIDS
DOC. NO. CPI: C2001-193312
TITLE: Inducing angiogenesis in a mammal required in physiological processes and in treating pathophysiologies such as reproduction, wound healing, ischemic heart disease, by **administering** a morphogenic **protein**
.
DERWENT CLASS: B04 D16
INVENTOR(S): RAMOSHEBI, L N; RIPAMONTI, U
PATENT ASSIGNEE(S): (STYC) STRYKER CORP; (RAMO-I) RAMOSHEBI L N; (RIPA-I) RIPAMONTI U
COUNTRY COUNT: 24
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

WO 2001074379 A2 20011011 (200175)* EN 81
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
W: AU CA JP
AU 2001050962 A 20011015 (200209)
EP 1267910 A2 20030102 (200310) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
US 2003104977 A1 20030605 (200339)
JP 2003528922 W 20030930 (200365) 76

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001074379	A2	WO 2001-US9451	20010323
AU 2001050962	A	AU 2001-50962	20010323
EP 1267910	A2	EP 2001-924295	20010323
		WO 2001-US9451	20010323
US 2003104977	A1	US 2000-540466	20000331
JP 2003528922	W	JP 2001-572121	20010323
		WO 2001-US9451	20010323

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001050962	A	Based on	WO 2001074379
EP 1267910	A2	Based on	WO 2001074379
JP 2003528922	W	Based on	WO 2001074379

PRIORITY APPLN. INFO: US 2000-540466 20000331
AN 2001-656972 [75] WPIDS
AB WO 200174379 A UPAB: 20011220
NOVELTY - Inducing (M1) angiogenesis in a mammal by **administering** a morphogenic **protein** (I), which is not bone morphogenic **protein** (BMP)-2 or GDF-5.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for improving (M2) the angiogenic inductive activity of (I) in a mammal by co **administering** a morphogenic **protein** stimulatory factor (MPSF) with (I).

ACTIVITY - Vulnerary; Vasotropic; Antianginal; Immunosuppressive; Osteopathic; Cardiant.

MECHANISM OF ACTION - Angiogenesis inducer (claimed). The single application of the morphogens pTGF- beta 1 (20 ng), bFGF (500 ng) or hOP-1 (100 and 1000 ng) and the binary application of hOP-1/bFGF (100/100 ng) or hOP-1/pTGF- beta 1 (100/5 and 100/20 ng) on the chick chlorioallantoic membrane (**CAM**) demonstrated significantly higher positive angiogenic scores compared to the BSA (bovine serum albumin) (500 ng) controls. The hOP-1/bFGF and hOP-1/pTGF- beta 1 combinations elicited the highest number of positive responses. The highest number of questionable angiogenic responses was produced by the lower dose of hOP-1 (100 ng). The morphogens also exhibited lower non-responsive angiogenic scores compared to the controls, with the hOP-1/pTGF- beta 1 combinations eliciting the loses number of non-responsive scores.

USE - (M1) is useful for inducing angiogenesis in a mammal (claimed) required in physiological processes and treating pathophysiologies such as reproduction, wound healing, organ transplantation, bone repair, ischemic heart disease and ischemic

peripheral vascular disease. (M2) is useful for improving angiogenic inductive activity of (I) in a mammal (claimed).
Dwg.0/10

L9 ANSWER 23 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-602600 [68] WPIDS
DOC. NO. CPI: C2001-178490
TITLE: New arginine-rich **peptides**, useful as **vascular endothelial growth** factor **inhibitors** for **treating cancers** and other **angiogenesis**-related diseases such as rheumatoid arthritis and diabetic retinopathy.
DERWENT CLASS: B04
INVENTOR(S): BAE, D G; CHAE, C B; YOON, W H
PATENT ASSIGNEE(S): (GREC) KOREA GREEN CROSS CORP; (POST-N) POSTECH FOUND
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001066127	A1	20010913	(200168)*	EN	40
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA JP US					
EP 1162991	A1	20011219	(200206)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001066127	A1	WO 1999-KR796	19991221
EP 1162991	A1	EP 1999-960007	19991221
		WO 1999-KR796	19991221

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1162991	A1	Based on	WO 2001066127

PRIORITY APPLN. INFO: WO 1999-KR796 19991221
AN 2001-602600 [68] WPIDS
AB WO 200166127 A UPAB: 20011121
NOVELTY - New **peptide** for inhibiting the activity of the **vascular endothelial growth** factor (**VEGF**), consists of six **amino** acid residues comprising arginine at the first, the fourth and the sixth positions from the **amino** end, one selected from arginine, lysine, and histidine at the second position, and one selected from arginine and lysine at the third and the fifth positions.
ACTIVITY - Cytostatic; antidiabetic; ophthalmological; antiarthritic.
MECHANISM OF ACTION - **VEGF** inhibitor.
To examine the ability of the **peptides** to **inhibit angiogenesis** induced by **VEGF**, fertilized eggs were incubated at 37 deg. C under a humidity of 90%.

After three days of culturing, the eggs were deprived of about 2 ml of albumin. After four days, eggs were partially deprived of the sheath to make a window with a size of 2 x 2 cm. After **VEGF** (10 ng/egg) was mixed with various amounts of **peptides** or other samples, 3 micro l of each mixture was dropped onto 1-4 fraction pieces of thermanox coverslips and dried. The pieces were placed on **CAM** of 9-day embryonic eggs. 2 Days later, the samples were independently observed under anatomical microscopes by two different persons to determine whether new blood vessels were induced by the dropped samples or not. In this regard, the experiment was repeated at least three times using 10 or more eggs per sample. Results showed that **VEGF** induced angiogenesis at a proportion of 33.6% in the italic model test. This angiogenic activity was effectively reduced to about 15.6% when egg samples were treated with the **peptides** (1 micro g/egg), along with **VEGF** and to about 18.8% when egg samples were treated with protamine (50 micro g/egg), known as an anti-angiogenic factor, along with **VEGF**.

USE - For **treating cancer** and **angiogenesis**-related diseases (claimed). For **inhibiting** the growth and **metastasis** of **cancer** cells. Angiogenesis related diseases include diabetic retinopathy and rheumatoid arthritis.

The effect of the **peptides** on human colon carcinoma cells (HM7) was examined. 5x106 HM7 cells were added, together with 0.5 micro g/ micro l of an **amino** acid sequence EEFDDA or RRKRRR (Sequence No.1), to a serum-free DMEM and introduced into 4 week-old male mice (athymic nude mice, BALB/c/nu/nu) by subcutaneous injection. From the next day, a solution of each **peptide** in PBS (0.5 micro g/100 micro l/day) was subcutaneously injected to the mice for 15 days. After 15 days of subcutaneous injection, the sequence EEFDDA exhibited no effects whereas the **peptide** RRKRR decreased tumor size by 28% compared to the control (PBS). RRKRR also exhibited high inhibitory effects and after 14 days reduced the number of metastatic nodules by 16 and 33% compared to a control in a similar assay where cancerous cells were transplanted into the spleen of 4 week-old BALB/c/nu/nu mice.

ADVANTAGE - The **peptides** have a superior ability to inhibit the binding of **VEGF** to its receptors. The **peptides** inhibit the growth of host normal cells (vascular endothelial cells), but not cancer cells themselves, and thus overcome the problems of conventional **therapies** for **cancer**, which are due to the versatility and resistance of cancer cells. In acute toxicity tests using SD rats, suspensions of the **peptides administered** at 1 mg/kg caused no sudden death nor clinical symptoms, and there were no toxicity signs in terms of e.g. weight change, serological tests or serobiochemical tests. Italic cytotoxicity tests also revealed that the **peptides** damage neither endothelial cells, human fibrosarcoma cells nor human colon carcinoma cells. The **peptides** were found to be safe with a lethal dose (LD50) of at least 1 mg/kg when **administered** via a non-oral route.
Dwg.0/20

L9 ANSWER 24 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-290891 [30] WPIDS
DOC. NO. CPI: C2001-089247
TITLE: Modulating cell phenotype in a patient having or

risk of developing a disease/condition linked with disregulation of cellular phenotype, comprises **administering** nucleic acid encoding cyclic-AMP responsive element binding **protein.**

DERWENT CLASS: B04
INVENTOR(S): KLEMM, D J; REUSCH, J E
PATENT ASSIGNEE(S): (NAJE-N) NAT JEWISH MEDICAL & RES CENT; (UYTE-N) UNIV TECHNOLOGY CORP; (USGO) US DEPT VETERANS AFFAIRS
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001029062	A2	20010426	(200130)*	EN	155

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001010829 A 20010430 (200148)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001029062	A2	WO 2000-US28316	20001012
AU 2001010829	A	AU 2001-10829	20001012

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001010829	A	Based on	WO 2001029062

PRIORITY APPLN. INFO: US 1999-420060 19991018
AN 2001-290891 [30] WPIDS
AB WO 200129062 A UPAB: 20010603
NOVELTY - Modulating (I) the phenotype of a target cell population in a patient, comprises **administering** a composition containing a recombinant nucleic acid molecule (rNA) with a nucleic acid sequence encoding a cyclic-AMP responsive element binding (CREB) **protein** having CREB biological activity operatively linked to a transcription control sequence.

DETAILED DESCRIPTION - Modulating (I) the phenotype of a target cell population in a patient, comprises **administering** a composition containing a recombinant nucleic acid molecule (rNA) with a nucleic acid sequence encoding a cyclic-AMP responsive element binding (CREB) **protein** having CREB biological activity operatively linked to a transcription control sequence, where the CREB **protein** is expressed by the recombinant nucleic acid in target cells, including cells deficient in endogenous CREB expression or biological activity and cells having normal endogenous CREB expression and biological activity which are predisposed to become deficient in endogenous CREB expression or

biological activity. INDEPENDENT CLAIMS are also included for the following:

(1) restoring the ability of a cell to differentiate, by transfecting the cell (not fully differentiated) deficient in CREB expression or biological activity with rNA encoding CREB;

(2) treating diabetes by **administering** a composition comprising rNA encoding CREB;

(3) **inhibiting** (II) **tumor** neovascularization in a patient, by **administering** a composition comprising a rNA encoding CREB having dominant negative CREB biological activity, which is expressed in fibroblasts and endothelial cells in or near a **tumor** in a patient and **inhibiting** neovascularization; and

(4) decreasing total body adiposity by **administering** to the patient, a composition comprising rNA encoding CREB having dominant negative CREB biological activity operatively linked to a transcription control sequence, where the CREB **protein** is expressed by the rNA in adipocytes of the patient, and expression of CREB in the adipocytes is sufficient to inhibit differentiation of the adipocytes.

ACTIVITY - Antidiabetic; **antitumor**; cytostatic; neuroprotective; nootropic; osteopathic; antiarthritic; antiparkinsonian; antianginal; antiatherosclerotic; vasotropic; cardiant; cerebroprotective; antidepressant; hypotensive. No biological data is given.

MECHANISM OF ACTION - Cell phenotype modulator. The impact of adenoviral infection with constitutively active CREB (adVP16 CREB) on CRE driven gene expression, proliferation and migration was studied. The functional consequences of infection with adVP16 CREB construct, its ability to drive transcription of an exogenous CREB-dependent promoter-reporter construct (CREluc), and its ability to induce CREB-dependent ICER (Inducible cAMP early repressor) gene expression in smooth muscle cell (SMC) was examined. SMC infected with 0-300 micro l of crude adVP16CREB were lyzed and assessed for **protein** content of the CREB dependent gene ICER. The results showed that ICER content increased with increasing doses of adVP16CREB. SMC transiently transfected with a CREluc reporter construct were infected with 300 micro l of crude adVP16CREB and assessed for reporter activation and adVP16CREB infection led to a significant increase in luciferase activity relative to that seen with adBetaGal. To assess the impact of adVP16CREB infection on SMC phenotype, **bovine aorta** SMC (BASMC) were grown to 70 % confluence and serum starved for 48 hours and were treated with 0.1 micro M platelet derived growth factor (PDGF) and assessed for thymidine incorporation and migration. Rates of DNA synthesis in cultured SMC cells were estimated. The results showed that adVP16CREB decreased PDGF-stimulated thymidine incorporation and cell migration in SMC. Treatment of SMC with high glucose for 48 hours resulted in increased cell migration and also infection with adVP16CREB attenuated glucose-induced acceleration of cell migration. These studies clearly demonstrated that constitutively active CREB promoted a more highly differentiated phenotype.

USE - (I) is useful for modulating the phenotype of a target cell population such as adipocytes, vascular smooth muscle cells, cardiomyocytes, hepatocytes, skeletal muscle, beta -cells, pituitary, synovial lining, ovarian, testicular, fibroblasts, endothelial, neural cells (dopaminergic neural transplant cells), hippocampal neurons, cells of cortex and basal ganglia in a patient

having or risk of developing atherosclerosis, angina, acute myocardial infarction, stroke, pulmonary hypertension, osteoarthritis, amputation from peripheral vascular disease, heart failure, spinal transection, acute neuronal ischemia, Alzheimer's, Parkinson's disease, depression or post-angioplasty restenosis. The method is useful for treating diabetes (all claimed). Dwg.0/14

L9 ANSWER 25 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-257785 [26] WPIDS
DOC. NO. CPI: C2001-077652
TITLE: **Peptides** comprising a portion of a **protein** selected from **plasminogen**, **endostatin, VEGF**, FLT-1 and **KDR/FLK-1** are useful for **treating** primary **tumor** growth.
DERWENT CLASS: B04
INVENTOR(S): KINI, R M; RUOWEN, G; GE, R
PATENT ASSIGNEE(S): (UYSI-N) UNIV SINGAPORE NAT
COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001018030	A2	20010315	(200126)*	EN	34
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CN JP					
SG 87828	A1	20020416	(200240)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001018030	A2	WO 2000-SG131	20000901
SG 87828	A1	SG 1999-4310	19990903

PRIORITY APPLN. INFO: SG 1999-4310 19990903
AN 2001-257785 [26] WPIDS
AB WO 200118030 A UPAB: 20030906
NOVELTY - **Peptides** (I) comprising a portion of a **protein** selected from **plasminogen, endostatin, VEGF**, FLT-1 and **KDR/FLK-1** are 7-20 **amino** acids long and exhibit an IC50 of 20 micro M or less in a **bovine aorta** endothelial cell proliferation assay or exhibit **inhibition** of **angiogenesis** in a **chick chorioallantoic** membrane assay of at least 30 % at a dose of 50 micro g/coverslip.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for a method of **preventing** or **treating** primary **tumor** growth or **metastasis** or undesired angiogenesis by **administering** a composition comprising (I).

ACTIVITY - Cytostatic.

Tests to determine the peptidic activity in **inhibiting angiogenesis** in the in vitro **bovine aorta**

endothelial (**BAE**) cell proliferation assay are described with Thr-Pro-His-Thr-His-Asn-Arg-Thr-Pro-Glu (seq. 3) having an IC50 of 20 pM.

MECHANISM OF ACTION - None given.

USE - (I) are used to **prevent** or **treat** primary **tumor** growth or **metastasis** or undesired angiogenesis.

ADVANTAGE - Compositions comprising (I) are effective in **inhibiting** undesirable **angiogenesis**. The small **peptides** have the ability to inhibit **bovine aorta** endothelial cell proliferation in the presence of basic Fibroblast Growth Factor in vitro. They can also **inhibit angiogenesis** in **chick chorioallantoic** membrane in vivo.

Dwg.0/12

L9 ANSWER 26 OF 37 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2001609917 MEDLINE
DOCUMENT NUMBER: 21540685 PubMed ID: 11683633
TITLE: p22 is a novel **plasminogen** fragment with **antiangiogenic** activity.
AUTHOR: Kwon M; Yoon C S; Fitzpatrick S; Kassam G; Graham K S; Young M K; Waisman D M
CORPORATE SOURCE: Cancer Biology Research Group, Department of Biochemistry & Molecular Biology, University of Calgary, Calgary, Alberta, Canada T2N 4N1.
SOURCE: BIOCHEMISTRY, (2001 Nov 6) 40 (44) 13246-53. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011102
Last Updated on STN: 20020123
Entered Medline: 20011207

AB Tumor or tumor-associated cells cleave circulating **plasminogen** into three or four kringle-containing **antiangiogenic** fragments, collectively referred to as angiostatin. Angiostatin blocks **tumor** growth and **metastasis** by **preventing** the growth of endothelial cells that are critical for tumor vascularization. Here, we show that cancer and normal cells convert **plasminogen** into a novel 22 kDa fragment (p22). Production of this **plasminogen** fragment in a cell-free system has allowed characterization of the structure and activity of the **protein**. p22 consists of **amino** acid residues 78-180 of **plasminogen** and therefore embodies the first **plasminogen** kringle (residues 84-162) as well as additional N- and C-terminal residues. Circular dichroism and intrinsic fluorescence spectrum analysis have defined structural differences between p22 and recombinant **plasminogen** kringle 1 (rK1), therefore suggesting a unique conformation for kringle 1 within p22. Proliferation of capillary endothelial cells but not cells of other lineages was selectively inhibited by p22 in vitro. In addition, p22 prevented vascular growth of **chick chorioallantoic** membranes (**CAMs**) in vivo. Furthermore, **administration** of p22 at low dose suppressed the growth of murine Lewis lung carcinoma

(LLC) metastatic foci in vivo. This is the first identification of a single kringle-containing **antiangiogenic plasminogen** fragment produced under physiological conditions.

L9 ANSWER 27 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001421508 EMBASE

TITLE: **Vascular endothelial growth** factor (**VEGF**) receptor-2 antagonists inhibit **VEGF**- and basic fibroblast growth factor-induced angiogenesis in vivo and in vitro.

AUTHOR: Tille J.-C.; Wood J.; Mandriota S.J.; Schnell C.; Ferrari S.; Mestan J.; Zhu Z.; Witte L.; Pepper M.S.

CORPORATE SOURCE: Dr. M.S. Pepper, Department of Morphology, University Medical Center, 1 Rue Michel Servet, 1211 Geneva 4, Switzerland. michael.pepper@medecine.unige.ch

SOURCE: Journal of Pharmacology and Experimental Therapeutics, (2001) 299/3 (1073-1085).
Refs: 42
ISSN: 0022-3565 CODEN: JPETAB

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Exponential tumor growth is angiogenesis-dependent. **Vascular endothelial growth** factor (**VEGF**) and basic fibroblast growth factor (bFGF) are potent angiogenic inducers that act synergistically in vivo and in vitro. We assessed the effect of specific inhibitors of **VEGF** receptor (VEGFR)-2 tyrosine kinase activity in in vivo and in vitro models of **VEGF**- and bFGF-induced angiogenesis. In an implant mouse model of **angiogenesis**, VEGFR-2 **inhibitors** completely blocked **angiogenesis** induced by **VEGF**, and, surprisingly, also inhibited the effect of bFGF to various extents. In vitro, **VEGF**- and bFGF-induced bovine microvascular and aortic endothelial (BME and **BAE**) cell collagen gel invasion could be blocked by the VEGFR-2 inhibitors by 100 and .apprx.90%, respectively. Similar results were obtained with VEGFR-1-IgG and VEGFR-3-IgG fusion **proteins** and with VEGFR-2 blocking antibodies. Both BME and **BAE** cells produce **VEGF** and **VEGF**-C, which is not modulated by bFGF. Thus, the unexpected **inhibition** of bFGF-induced **angiogenesis** by VEGFR-2 antagonists reveals a requirement for endogenous **VEGF** and **VEGF**-C in this process. These findings broaden the spectrum of mediators of **angiogenesis** that can be **inhibited** by VEGFR-2 antagonists and highlight the importance of these compounds as agents for **inhibiting tumor** growth sustained by both **VEGF** and bFGF.

L9 ANSWER 28 OF 37 MEDLINE on STN

ACCESSION NUMBER: 2002100267 MEDLINE

DOCUMENT NUMBER: 21657305 PubMed ID: 11798517

TITLE: In vivo absence of synergism between fibroblast growth factor-2 and **vascular endothelial growth** factor.
AUTHOR: Nico B; de Falco G; Vacca A; Roncali L; Ribatti D
CORPORATE SOURCE: Department of Human Anatomy and Histology, University of Bari Medical School, Bari, Italy.
SOURCE: J Hematother Stem Cell Res, (2001 Dec) 10 (6) 905-12. Journal code: 100892915. ISSN: 1525-8165.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20020208
Last Updated on STN: 20021211
Entered Medline: 20030411

AB Fibroblast growth factor-2 (FGF-2) and **vascular endothelial growth** factor (**VEGF**) are potent angiogenesis inducers in vivo and in vitro and may act in synergy. This possibility has been investigated by their simultaneous **administration** in the **chick** embryo **chorioallantoic** membrane (**CAM**) assay. Macroscopic and microscopic quantification of the angiogenic response 4 days after **administration** clearly demonstrated the absence of synergism. When FGF-2 or **VEGF** concentration was fixed at 0.25 microg/embryo, the simultaneous addition of increasing concentration (0.25, 0.50, 1.0 microg/embryo) of **VEGF** or FGF-2 did not stimulate a synergistic dose-dependent angiogenic response. In both conditions, the angiogenic response overlapped that induced by the two growth factors **administered** alone. It is suggested that exogenous **administration** of FGF-2 and **VEGF** in the **CAM** assay may induce an activation of endogenous angiogenic factors, such as FGF-2, and endogenous **inhibitors** of **angiogenesis**, such as nitric oxide, normally expressed in the **CAM** during the development of its vascular tree. Thus, in an in vivo system, evaluation of synergistic action between two cytokines and discrimination of their specific activity are more difficult than in an in vitro assay.

L9 ANSWER 29 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-025089 [03] WPIDS
DOC. NO. CPI: C2001-007725
TITLE: Lipid formulation for **treating** a hyperproliferative disorder, such as **cancer**, arthritis or psoriasis, comprises 1,2-bis(oleoyloxy)-3-(trimethyl ammono)propane and cholesterol, or a derivative or mixture, in combination with a nucleic acid.
DERWENT CLASS: B04 D16
INVENTOR(S): RAMESH, R; ROTH, J A; SAEKI, T; WILSON, D
PATENT ASSIGNEE(S): (INTR-N) INTROGEN THERAPEUTICS INC; (TEXA) UNIV TEXAS SYSTEM
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000071096	A2	20001130	(200103)*	EN	148

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC
MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK
DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL
PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU
ZA ZW

AU 2000051618 A 20001212 (200115)
EP 1180016 A2 20020220 (200221) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK
NL PT RO SI

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000071096	A2	WO 2000-US14350	20000524
AU 2000051618	A	AU 2000-51618	20000524
EP 1180016	A2	EP 2000-936279	20000524
		WO 2000-US14350	20000524

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000051618	A	Based on	WO 2000071096
EP 1180016	A2	Based on	WO 2000071096

PRIORITY APPLN. INFO: US 1999-135818P 19990524
AN 2001-025089 [03] WPIDS
AB WO 200071096 A UPAB: 20011129
NOVELTY - A pharmaceutically acceptable lipid formulation (F) comprising 1,2-bis(oleoyloxy)-3-(trimethyl ammono)propane (DOTAP) and at least one cholesterol or cholesterol derivative or mixture in combination with a nucleic acid is new.

DETAILED DESCRIPTION - A new pharmaceutically acceptable lipid formulation comprises DOTAP and at least one cholesterol or cholesterol derivative or mixture in combination with:

(1) an antisense or ribozyme nucleic acid molecule that inhibits the expression of a growth-promoting **polypeptide**; or

(2) a nucleic acid under the control of a promoter and encoding

(i) an anti-proliferative **polypeptide**; or

(ii) an antisense molecule or ribozyme that inhibits the expression of a growth-promoting **protein**.

An INDEPENDENT CLAIM is also included for treating a hyperproliferative disorder comprising **administering** an effective amount of (F) to a patient in need of anti-proliferative therapy.

ACTIVITY - Cytostatic; antiarthritic; antirheumatic; antiinflammatory; osteopathic; vasotropic; antipsoriatic.

The ability of a DOTAP:Chol-p53 DNA:liposome complex to suppress the growth of p53 gene-null H1299 human lung subcutaneous tumors in nu/nu mice was assessed. Tumor-bearing mice were divided into 3 groups. One group received no treatment, one treatment with naked p53 plasmid DNA and one with DOTAP:CHol-p53 liposome complex daily for a total of six doses (100 micro g/dose). **Tumor** growth was significantly **inhibited** in mice **treated**

with the complex (**tumor** volume and size were about 25 and 150 mm3, respectively, 16 days after initial dose) compared with **tumor** growth in the no **treatment** and p53 plasmid DNA control groups (tumor volume and size were about 350 and 325 mm3, respectively, 16 days after initial dose).

MECHANISM OF ACTION - Gene therapy. No suitable biological data is given.

USE - (F) is used to **treat** a hyperproliferative disorder, such as, **cancer** (preferably lung, head and neck, pancreatic, prostate, renal, bone, testicular, breast, cervical, gastrointestinal, lymphoma, brain, breast, ovarian, leukemia, myeloma, colorectal, esophageal, skin, thyroid, liver, or bladder cancer), rheumatoid arthritis, inflammatory bowel disease, osteoarthritis, adenoma, leiomyoma, lipoma, hemangioma, fibroma, restenosis, preneoplastic lesions, vascular occlusions, or psoriasis (claimed).

ADVANTAGE - The lipid formulation is used for nonviral gene therapy which reduces the disadvantages of:

(1) the potential for a patient immune response;

(2) a possible inability to repeat **administration** of viral vectors;

(3) a difficulty in generating high titers; and

(4) the potential of infectious virus production.

(F) enhances systemic in vivo gene transfer by approximately 150 fold. BALB/c nude mice were injected with adenovirus (Ad)- beta gal at 109 plaque forming units (pfu), beta gal DNA at 100 micro g/200 micro l volume and lipid complex- beta gal at 100 micro g/5mM lipids in a 200 micro l volume. Lung tissue from the mice was examined under a microscope. Ad- beta gal treated animals had an increase in positive cells of 4 % over background and lipid complex-beta gal treated animals had an increase in positive cells of 11 % over background. In vivo **administration** of lipid complex-beta gal transfects lung cells with a higher efficiency than Ad-beta gal.

Dwg.0/3

L9 ANSWER 30 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2000-524487 [47] WPIDS

DOC. NO. CPI: C2000-155811

TITLE: Combined **administration** of an **angiogenesis inhibiting** agent and an anti-**tumor** immunotherapeutic agent used for **inhibiting tumor** cell proliferation.

DERWENT CLASS: B04

INVENTOR(S): CHERESH, D A; GILLIES, S D; LODE, H N; REISFELD, R A

PATENT ASSIGNEE(S): (LEXI-N) LEXIGEN PHARM CORP; (SCRI) SCRIPPS RES INST

COUNTRY COUNT: 91

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000047228	A1	20000817	(200047)*	EN	78

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM

EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ
LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU
SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000032280 A 20000829 (200062)
NO 2001003906 A 20011009 (200174)
EP 1156823 A1 20011128 (200201) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK
NL PT RO SE SI
KR 2001102043 A 20011115 (200231)
BR 2000008161 A 20020528 (200239)
CZ 2001002791 A3 20020515 (200241)
SK 2001001113 A3 20020604 (200247)
HU 2002000128 B 20020528 (200249)
CN 1346279 A 20020424 (200251)
JP 2002536419 W 20021029 (200274) 73
ZA 2001006455 A 20030129 (200314) 90
MX 2001008110 A1 20021001 (200370)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000047228	A1	WO 2000-US3483	20000211
AU 2000032280	A	AU 2000-32280	20000211
NO 2001003906	A	WO 2000-US3483	20000211
		NO 2001-3906	20010810
EP 1156823	A1	EP 2000-910138	20000211
		WO 2000-US3483	20000211
KR 2001102043	A	KR 2001-710132	20010810
BR 2000008161	A	BR 2000-8161	20000211
		WO 2000-US3483	20000211
CZ 2001002791	A3	WO 2000-US3483	20000211
		CZ 2001-2791	20000211
SK 2001001113	A3	WO 2000-US3483	20000211
		SK 2001-1113	20000211
HU 2002000128	B	WO 2000-US3483	20000211
		HU 2002-128	20000211
CN 1346279	A	CN 2000-806134	20000211
JP 2002536419	W	JP 2000-598179	20000211
		WO 2000-US3483	20000211
ZA 2001006455	A	ZA 2001-6455	20010806
MX 2001008110	A1	WO 2000-US3483	20000211
		MX 2001-8110	20010810

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000032280	A	Based on	WO 2000047228
EP 1156823	A1	Based on	WO 2000047228
BR 2000008161	A	Based on	WO 2000047228
CZ 2001002791	A3	Based on	WO 2000047228
SK 2001001113	A3	Based on	WO 2000047228
HU 2002000128	B	Based on	WO 2000047228
JP 2002536419	W	Based on	WO 2000047228
MX 2001008110	A1	Based on	WO 2000047228

PRIORITY APPLN. INFO: US 1999-119721P 19990212

Searcher : Shears 571-272-2528

AN 2000-524487 [47] WPIDS
AB WO 200047228 A UPAB: 20011129
NOVELTY - **Treating** a **tumor** cell in a patient with an **angiogenesis inhibiting** agent and an anti-**tumor** immunotherapeutic agent which comprises a cell-effector component and a **tumor** associated antigen targeting component **inhibits tumor** cell proliferation.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition comprising at least one **angiogenesis inhibiting** agent and at least one anti-tumor immunotherapeutic agent which comprises a cell-effector component joined to a tumor associated antigen targeting component; and

(2) a kit for **treating** a **tumor** cell or **tumor metastases** comprising a package containing an **angiogenesis inhibiting** agent and an anti-**tumor** immunotherapeutic agent which comprises a cell-effector component and a tumor associated antigen targeting component.

ACTIVITY - Cytostatic.

Sequential combination of anti-angiogenic alpha v integrin antagonist and anti-tumor compartment-specific immunotherapy with antibody-IL-2 fusion **protein** was carried out on spontaneous hepatic neuroblastoma **metastases**. Anti-vascular **treatment** was carried out for 10 days in mice with established primary tumors. After surgical removal of primary tumors, mice received the tumor compartment-specific immunotherapy by daily intravenous injection of 5 micro g ch14.18-IL-2 fusion **protein** (x5). The number of spontaneous liver metastases was determined by macroscopic counts of liver foci. Only mice which had been treated sequentially with both agents presented a 1.5-2 log decrease in hepatic metastases in contrast to all controls, where treatment with each agent used as monotherapy was ineffective. Four of eight mice subjected to the combined **therapy** showed complete absence of hepatic **metastases** and the remaining animals showed only 1-5 small metastic lesions. Similar results were obtained from simultaneous combinations of the integrin alpha v antagonist with the ch14.18-IL-2 fusion **protein**.

MECHANISM OF ACTION - alpha v beta 3 antagonist.

USE - Combined **administration** of the **angiogenesis inhibiting** agent and anti-**tumor** immunotherapeutic agent is used to **inhibit** the proliferation of **tumor** cells in primary **tumors** and **metastases** (claimed). The **treatment** can also **inhibit** the formation of additional **tumor metastases** and lead to **tumor** cell death. The **angiogenesis inhibiting** agent **inhibits** the formation of new blood vessels or the enlargement of existing capillary networks into the tissues near a tumor cell.

ADVANTAGE - The tumor compartment specific response is directed to the tumor microenvironment by the tumor associated antigen targeting component.

Dwg.0/4

L9 ANSWER 31 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-452382 [39] WPIDS

DOC. NO. CPI: C2000-137931
TITLE: Expression vector comprising multiple shear stress response elements, useful for modulating endothelial cell proliferation, stimulating or down-regulating **angiogenesis** and **treating** vasculogenic/**angiogenic** disorders.
DERWENT CLASS: B04 D16
INVENTOR(S): RESNICK, N
PATENT ASSIGNEE(S): (FLOR-N) FLORENCE MEDICAL LTD
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000039275	A2	20000706	(200039)*	EN	61
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000017954	A	20000731	(200050)		
EP 1141266	A2	20011010	(200167)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
US 6440726	B1	20020827	(200259)		
JP 2002533113	W	20021008	(200281)		73

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000039275	A2	WO 1999-IL702	19991223
AU 2000017954	A	AU 2000-17954	19991223
EP 1141266	A2	EP 1999-961261	19991223
		WO 1999-IL702	19991223
US 6440726	B1	US 1998-220510	19981224
JP 2002533113	W	WO 1999-IL702	19991223
		JP 2000-591168	19991223

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000017954	A	Based on	WO 2000039275
EP 1141266	A2	Based on	WO 2000039275
JP 2002533113	W	Based on	WO 2000039275

PRIORITY APPLN. INFO: US 1998-220510 19981224; US 1998-113863P 19981224
AN 2000-452382 [39] WPIDS
AB WO 200039275 A UPAB: 20000818
NOVELTY - A vector (I) comprising a multiple number of nucleic acids of promoter Shear Stress Response Elements (SSRE) and one or more genes, or a nucleic acid of an antisense molecule, ribozyme, double stranded RNA, or a nucleic acid which encodes for a repressor antibody, mutant **protein** which inhibits the synthesis of,

or activity of the **protein** or **peptide**, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a host cell comprising (I); and

(2) a method for screening (III) test compound for their ability to regulate angiogenesis and/or vasculogenesis, comprising:

(a) contacting endothelial cells with the compound to be tested;

(b) assaying the amount of angiogenesis and/or vasculogenesis produced as a result of the test compound;

(c) stimulating endothelial cells by introducing (I);

(d) assaying the amount of angiogenesis and/or vasculogenesis produced as a result of the vector;

(e) comparing the amount of angiogenesis and/or vasculogenesis produced as a result of (b) to that of (d), where an increased amount of angiogenesis and/or vasculogenesis of the test compound indicates that the test compound regulates angiogenesis and/or vasculogenesis.

ACTIVITY - Cytostatic; Cardiant; Vasotropic; Vulnerary; Antidiabetic; Antiatherosclerotic; Hypotensive; Antilipemic.

MECHANISM OF ACTION - Gene therapy.

No supporting biological data is provided.

USE - (I) is useful for stimulating or inhibiting vascular endothelial cell or capillary endothelial cell proliferation and for stimulating angiogenesis in cells. (I) or (II) is useful for modulating vascular permeability in a mammal, for stimulating or inhibiting the formation, maturation or regression of blood vessels, modulating genes or **proteins** involved in a diseases, down regulating **angiogenesis** and for **treating** vasculogenic and/or **angiogenic** disorders. These disorders include cardiovascular disorder, neoplastic disorders, ischemia, atherosclerosis, hypertension, diabetes, hypercholesterolemia and wound healing.

(II) is **administered** to the mammal in the vasculature such that the vasculature has shear stress forces to permit SSRE to be activated by the shear stress and transcriptionally regulate endothelial cell gene expression. Down regulation of angiogenesis further comprises **administering** an inflammatory agent, vasodilator, fibrinolytic activators, tumor necrosis factor (TNF) or thrombotic factors or an agent which acts as a vasoconstrictor.

(I) is also useful for detecting shear stress or shear stress related condition in a subject, where the reporter gene in (I) is activated in shear stress environment indicating shear stress or its related condition. SSRE vectors are also useful for screening test compounds for their ability to regulate angiogenesis and/or vasculogenesis (all claimed).

Dwg.0/2

L9 ANSWER 32 OF 37 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-205996 [18] WPIDS
DOC. NO. CPI: C2000-063709
TITLE: Modulation of **angiogenesis** in mammals, useful for **treating** e.g. atherosclerosis, **tumors**, wounds, vascular disease, hypoxic tissue damage, ischemia, balloon angioplasty, frostbite, gangrene or poor circulation.
DERWENT CLASS: B04 D16
INVENTOR(S): HSIEH, C; LEE, M; MAEMURA, K; HIESH, C

PATENT ASSIGNEE(S): (HARD) HARVARD COLLEGE; (HSIE-I) HSIEH C; (LEEM-I) LEE M; (MAEM-I) MAEMURA K
COUNTRY COUNT: 88
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000009657	A2	20000224	(200018)*	EN	57

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 9955629	A	20000306	(200030)
US 6395548	B1	20020528	(200243)
US 2003032609	A1	20030213	(200314)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2000009657	A2		WO 1999-US18539	19990813
AU 9955629	A		AU 1999-55629	19990813
US 6395548	B1	Provisional	US 1998-96515P	19980814
			US 1999-374454	19990813
US 2003032609	A1	Provisional	US 1998-96515P	19980814
		Cont of	US 1999-374454	19990813
			US 2002-121235	20020412

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9955629	A	Based on	WO 2000009657
US 2003032609	A1	Cont of	US 6395548

PRIORITY APPLN. INFO: US 1998-96515P 19980814; US 1999-374454 19990813; US 2002-121235 20020412
AN 2000-205996 [18] WPIDS
AB WO 200009657 A UPAB: 20000412
NOVELTY - A novel method of **inhibiting** **angiogenesis** in a mammal comprises **administering** to the mammal a compound which inhibits binding of endothelial PAS domain **protein**-1 (EPAS1) to cis-acting transcription regulatory DNA of an angiogenic factor.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) an antibody which binds to EPAS1;
(2) a method of promoting angiogenesis in a mammal comprising **administering** to the mammal a compound which increases expression of **vascular endothelial** **growth** factor (**VEGF**) or a **VEGF**-receptor (**VEGF**-R) in an endothelial cell;
(3) a pure DNA comprising a sequence encoding an aryl hydrocarbon receptor nuclear translocator-4 (ARNT4) **polypeptide**;
(4) a pure DNA comprising a nucleotide sequence having at least

50% sequence identity to sequence (XX) shown;

(5) a pure DNA comprising a strand which hybridizes at high stringency to a strand of DNA consisting of the coding sequence (XX), or the complement;

(6) a pure DNA comprising sequence having at least 50% sequence identity to the coding sequence (XX), and encoding a **polypeptide** having the biological activity of an ARNT4 **polypeptide**;

(7) a pure ARNT4 **polypeptide**;

(8) a vector comprising DNA as in (3);

(9) a host cell comprising DNA as in (3);

(10) a transgenic non-human animal the germ cells and nucleated somatic cells of which comprise a null mutation in a gene encoding ARNT4;

(11) a method of **inhibiting angiogenesis** in a mammal comprising **administering** to the mammal a compound which inhibits binding of EPAS1 to ARNT4;

(12) an EPAS1 **polypeptide** lacking a transactivation domain;

(13) a nucleic acid encoding an EPAS1 **polypeptide** lacking the **amino** acid sequence (II)

EDYYTSLDNDLKIEVIEKLFAMDTEAKDQCSTQTDFNELDLETLAPYIPMDGEDFQLSPICPEERLLA
ENPQSTPQHCFSAMTNIFQPLAPVAPHSPFLLDKFQQQLESKKTEPEHRPMSSIFFDAGSKASLPPCC
GQASTPLSSMGGRSNTQWPPDPPLHFGPTKWAVGDQRTEFLGAAPLGPPVSPPHVSTFKTRSAKGFGA
R.

ACTIVITY - Cytostatic; Antiarteriosclerotic; Vulnerary; Cardiant; Vasotropic; Cerebroprotective.

MECHANISM OF ACTION - Modulators of angiogenesis.

EPAS1 and **KDR/flk-1** transcripts were found to colocalize in vascular endothelial cells in mouse embryonic and adult tissue. To study the expression of EPAS1 relative to **KDR/flk-1**, a plasmid containing 4.0 kb of human **KDR/flk-1** 5'-flanking sequence linked to the luciferase reporter gene and a second vector containing DNA encoding either EPAS1 or another bHLH-PAS domain transcription factor HIF-1 alpha were cotransfected into bovine aortic endothelial cells (**BAEC**). EPAS1 but not HIF-1 alpha markedly increased **KDR/flk-1** promoter activity in a dose-dependent manner, and this induction of the **KDR/flk-1** promoter by EPAS1 occurred preferentially in endothelial cells. In contrast, both EPAS1 and HIF-1 alpha activated the **VEGF** promoter in a non-endothelial cell-specific manner. This is the first demonstration of transactivation of the **KDR/flk-1** promoter by EPAS1. By regulating transcription of **KDR/flk-1** and **VEGF**, EPAS1 plays an important role in regulating vasculogenesis and angiogenesis.

USE - The methods can be used to **inhibit angiogenesis**, e.g. to **inhibit** the growth of an atherosclerotic lesion or **inhibit tumor** growth. The methods can also be used to enhance angiogenesis to promote non blood vessel formation, e.g. to promote angiogenesis in wound healing (e.g. healing or broken bones, burns, diabetic ulcers, or traumatic or surgical wounds) and organ transplantation. Such compounds may be used to treat peripheral vascular disease, cerebral vascular disease, hypoxic tissue damage (e.g. hypoxic damage to heart tissue), or coronary vascular disease as well as to treat

patients who have, or have had, transient ischemic attacks, vascular graft surgery, balloon angioplasty, frostbite, gangrene, or poor circulation. Modulation of ARNT4 production or activity can be used to regulate circadian rhythms, e.g. by forming a heterodimer with Clock, or to treat circadian rhythm disorders.
Dwg.0/6

L9 ANSWER 33 OF 37 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001077245 MEDLINE
DOCUMENT NUMBER: 21002564 PubMed ID: 11118060
TITLE: HGF/NK4, a four-kringle antagonist of hepatocyte growth factor, is an **angiogenesis inhibitor** that suppresses **tumor** growth and **metastasis** in mice.
AUTHOR: Kuba K; Matsumoto K; Date K; Shimura H; Tanaka M; Nakamura T
CORPORATE SOURCE: Department of Oncology, Biomedical Research Center, Osaka University Medical School, Suita, Japan.
SOURCE: CANCER RESEARCH, (2000 Dec 1) 60 (23) 6737-43. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010111

AB We reported that NK4, composed of the N-terminal hairpin and subsequent four kringle domains of hepatocyte growth factor (HGF), acts as the competitive antagonist for HGF. We now provide the first evidence that NK4 **inhibits tumor** growth and **metastasis** as an **angiogenesis inhibitor** as well as an HGF antagonist. **Administration** of NK4 suppressed primary tumor growth and lung metastasis of Lewis lung carcinoma and Jyg-MC(A) mammary carcinoma s.c. implanted into mice, although neither HGF nor NK4 affected proliferation and survival of these tumor cells in vitro. NK4 treatment resulted in a remarkable decrease in microvessel density and an increase of apoptotic tumor cells in primary **tumors**, which suggests that the **inhibition** of primary **tumor** growth by NK4 may be achieved by suppression of tumor angiogenesis. In vivo, NK4 **inhibited angiogenesis** in **chick chorioallantoic** membranes and in rabbit corneal neovascularization induced by basic fibroblast growth factor (bFGF). In vitro, NK4 inhibited growth and migration of human microvascular endothelial cells induced by bFGF and **vascular endothelial growth** factor (**VEGF**) as well as by HGF. HGF and **VEGF** activated the Met/HGF receptor and the KDR/**VEGF** receptor, respectively, whereas NK4 inhibited HGF-induced Met tyrosine phosphorylation but not **VEGF**-induced KDR phosphorylation. NK4 inhibited HGF-induced ERK1/2 (p44/42 mitogen-activated **protein** kinase) activation, but allowed for bFGF- and **VEGF**-induced ERK1/2 activation. These results indicate that NK4 is an **angiogenesis inhibitor** as well as an HGF antagonist, and that the **antiangiogenic** action of NK4 is independent of its activity as HGF antagonist. The bifunctional

properties of NK4 to act as an **angiogenesis inhibitor** and as an HGF antagonist raises the possibility that NK4 may prove **therapeutic** for **cancer** patients.

L9 ANSWER 34 OF 37 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1999318889 MEDLINE
DOCUMENT NUMBER: 99318889 PubMed ID: 10388598
TITLE: A comparison of two controlled-release delivery systems for the delivery of amiloride to control angiogenesis.
AUTHOR: Knoll A; Schmidt S; Chapman M; Wiley D; Bulgrin J; Blank J; Kirchner L
CORPORATE SOURCE: The Falor Center for Vascular Studies, Akron City Hospital, Summa Health System, 525 E. Market Street, Akron, Ohio 44309, USA.
SOURCE: MICROVASCULAR RESEARCH, (1999 Jul) 58 (1) 1-9. Journal code: 0165035. ISSN: 0026-2862.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990913
Last Updated on STN: 20000303
Entered Medline: 19990902

AB The diuretic amiloride has been reported to inhibit both Na+-H+ antiport and the urokinase-type **plasminogen** activator. As a consequence of these inhibitions, neovascularization may also be inhibited. We hypothesized that if amiloride could be effectively delivered in a site-specific manner, a system might be developed that could **inhibit** localized **angiogenesis**. In order to evaluate this possibility we conducted a study that compared two different controlled-release systems into which amiloride had been incorporated. The effectiveness of amiloride release from each delivery system was determined by quantitating angiogenic patterns in a **chick chorioallantoic** membrane (**CAM**) system using a fractal analysis software program. The two delivery systems compared were sucrose acetate isobutyrate (SAIB) and calcium alginate. Initial HPLC laboratory tests confirmed that amiloride could be released from both SAIB and calcium alginate in vitro in a sustained manner for 72 h. The **CAM** studies confirmed that neither SAIB nor calcium alginate alone promoted or **inhibited angiogenesis** when compared to nontreated controls. The release of amiloride from each delivery vehicle resulted in a significant ($P < 0.05$) **inhibition** of **angiogenesis** following both 24 and 48 h of release compared to controls. There was no difference in **inhibition** of **angiogenesis**, however, when comparing SAIB + amiloride **treated CAMs** with calcium alginate + amiloride treated **CAMs**. These data suggest that both SAIB and calcium alginate may be useful delivery vehicles for the localized application of amiloride to control angiogenesis. Such a system could potentially control tumor angiogenesis without systemic effects.

L9 ANSWER 35 OF 37 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

ACCESSION NUMBER: 1999:60673 SCISEARCH
THE GENUINE ARTICLE: 154RT
TITLE: Inhibitory effect of suramin in rat models of angiogenesis in vitro and in vivo
AUTHOR: Bocci G; Danesi R; Benelli U; Innocenti F; DiPaolo A; Fogli S; DelTacca M (Reprint)
CORPORATE SOURCE: UNIV PISA, DEPT ONCOL, DIV PHARMACOL & CHEMOTHERAPY, VIA ROMA 55, I-56126 PISA, ITALY (Reprint); UNIV PISA, DEPT ONCOL, DIV PHARMACOL & CHEMOTHERAPY, I-56126 PISA, ITALY; SCH UNIV STUDIES & DOCTORAL RES S ANNA, I-56100 PISA, ITALY; UNIV PISA, DEPT NEUROSCI, DIV OPHTHALMOL, I-56126 PISA, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (MAR 1998) Vol. 43, No. 3, pp. 205-212.
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.
ISSN: 0344-5704.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 37

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The aim of the present study was to test the ability of the chemotherapeutic agent suramin to **inhibit angiogenesis** in experimental models in vitro and in vivo. In the culture of rat aortic rings on fibronectin, suramin dose-dependently inhibited vascular cell growth, achieving the maximal effect (mean - 88% versus controls, P < 0.05) at 400 mu g/ml. Image analysis showed that suramin could inhibit microvessel sprouting in fibrin from rat aortic rings as evaluated by the ratio between the cellular area and the mean gray value of the sample (sprouting index); suramin at 50 mu g/ml significantly reduced the sprouting index from the control value of 0.35 +/- 0.04 to 0.14 +/- 0.02 mm(2)/gray level (P < 0.05). Likewise, the area occupied by cells was 19.2 +/- 1.8 mm(2) as compared with 41.8 +/- 4.2 mm(2) in controls (P < 0.05). In the rat model of neovascularization induced in the cornea by chemical injury, suramin at 1.6 mg/eye per day reduced the length of blood vessels (0.7 +/- 0.1 mm as compared with 1.5 +/- 0.1 mm in controls, P < 0.05). In the same model the ratio between the area of blood vessels and the total area of the cornea (area fraction score) was decreased by suramin from 0.19 +/- 0.02 in controls to 0.03 +/- 0.003 (P < 0.05). Suramin given i.p. at 30 mg/kg per day markedly inhibited the neovascularization induced in the rat mesentery by compound 48/80 or conditioned medium from cells secreting the angiogenic **protein** fibroblast growth factor-3 (FGF-3). The area fraction score in control rats treated with compound 48/80 was 0.31 +/- 0.03, and this was reduced to 0.07 +/- 0.01 by suramin (P < 0.05), After i.p. **administration** of FGF-3 the area fraction score was reduced by suramin from 0.29 +/- 0.03 to 0.05 +/- 0.01 (P < 0.05). These results provide evidence that suramin exerts **inhibitory** effects on **angiogenesis** in both in vitro and in vivo models.

L9 ANSWER 36 OF 37 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 96189310 MEDLINE
DOCUMENT NUMBER: 96189310 PubMed ID: 8640821
TITLE: **Vascular endothelial**

growth factor-toxin conjugate specifically inhibits **KDR/flk-1** -positive endothelial cell proliferation in vitro and angiogenesis in vivo.

AUTHOR: Ramakrishnan S; Olson T A; Bautch V L; Mohanraj D
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota, Minneapolis, 55455, USA.

CONTRACT NUMBER: CA-48068 (NCI)
HL43174 (NHLBI)
SOURCE: CANCER RESEARCH, (1996 Mar 15) 56 (6) 1324-30.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960726
Last Updated on STN: 20000303
Entered Medline: 19960715

AB **Inhibition** of **tumor** neovascularization has profound effects on the growth of solid tumors. An endothelial cell-specific cytotoxic conjugate was prepared by chemically linking recombinant **vascular endothelial growth** factor (VEGF165) and a truncated diphtheria toxin molecule (DT385). The treatment of subconfluent cultures of human umbilical vein endothelial cells and human microvascular endothelial cells with the VEGF165-DT385 conjugate resulted in a selective, dose-dependent inhibition of growth. Parallel experiments with either the free toxin or a mixture of **VEGF** and the toxin **polypeptide** did not affect proliferation (DNA synthesis) of these cells. The selective cytotoxicity correlated with the appropriate receptor expression (**KDR/flk-1** positive) on the target cells. **VEGF**-toxin conjugate inhibited the growth of a murine hemangioma-derived endothelial cell line (Py-4-1), which was positive for flk-1 expression. Under similar conditions, the conjugate did not affect the proliferation of a receptor-negative ovarian cancer cell line in vitro. In an in vivo model of angiogenesis, the VEGF165-DT385 conjugate blocked basic fibroblast growth factor-induced neovascularization of the **chick chorioallantoic** membrane. These studies demonstrate the successful targeting of a cytotoxic **polypeptide** to proliferating vascular endothelial cells (normal and tumorigenic) and the potential utility of such conjugates in blocking tumor neovascularization.

L9 ANSWER 37 OF 37 MEDLINE on STN
ACCESSION NUMBER: 93260040 MEDLINE
DOCUMENT NUMBER: 93260040 PubMed ID: 7684043
TITLE: Mechanism of action of angiostatic steroids: suppression of **plasminogen** activator activity via stimulation of **plasminogen** activator inhibitor synthesis.

AUTHOR: Blei F; Wilson E L; Mignatti P; Rifkin D B
CORPORATE SOURCE: Department of Pediatrics, New York University Medical Center, New York, New York.

CONTRACT NUMBER: 5 T32 GM 07552 (NIGMS)
CA 34282 (NCI)
CA 49419 (NCI)

+
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (1993 Jun) 155 (3) 568-78.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930625
Last Updated on STN: 20000303
Entered Medline: 19930617

AB Recently, a novel class of angiostatic steroids which block angiogenesis in several systems has been described. Since the elaboration of proteases is believed to be an important component of angiogenesis, we tested whether these steroids blocked the fibrinolytic response of endothelial cells to the angiogenic **protein**, basic fibroblast growth factor [bFGF]). Cultured bovine aortic endothelial (**BAE**) cells were incubated with bFGF and/or medroxyprogesterone acetate (MPA), an angiostatic steroid which has been shown to **inhibit** vascularization, collagenolysis, and **tumor** growth. When bFGF (3 ng/ml) was added to confluent monolayers of **BAE** cells, **plasminogen** activator (PA) activity in the medium was increased threefold. In contrast, MPA at 10(-6) M, 10(-7) M, 10(-8) M, and 10(-9) M decreased PA levels in the medium by 83%, 83%, 75%, and 39%, respectively. The stimulation of PA levels in **BAE** cells by bFGF (3 ng/ml) was abrogated by the presence of 10(-6) M MPA. This decrease in PA activity was found to be mediated by a significant increase in **plasminogen** activator inhibitor type-1 (PAI-1) production. MPA, therefore, negated one of the important enzymatic activities associated with the angiogenic process. In contrast to the decreased levels of secreted PA in cultures exposed simultaneously to MPA and bFGF, cell-associated PA levels remained high, consistent with earlier observations indicating that PAI-1 does not inhibit cell-associated PA. Thus, angiostatic steroids may exert their **inhibitory** effects on **angiogenesis** by increasing the synthesis of PAI-1. This, in turn, inhibits PA activity and, therefore, plasmin generation, which is essential for the invasive aspect of angiogenesis.

(FILE 'HCAPLUS' ENTERED AT 10:16:56 ON 06 FEB 2004)

L1 1108 SEA FILE=REGISTRY ABB=ON PLU=ON (PLASMINOGEN? OR ENDOSTATIN? OR VEGF? OR VASCULAR ENDOTHELIAL GROWTH FACTOR?)/CN

L2 36818 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR PLASMINOGEN OR PROFIBRINOLYSIN OR PRO FIBRINOLYSIN OR ENDOSTATIN OR VEGF OR VASCULAR ENDOTHELIAL GROWTH OR KDR(A)(FLK1 OR FLKI OR FLK(W)(1 OR I))

L3 5528 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND (ANGIOGEN? OR TUMOR OR TUMOUR OR METAST? OR NEOPLAS? OR CANCER? OR CARCIN?)(5A)(TREAT? OR THERAP? OR PREVENT? OR INHIBIT?)

L4 3090 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND (ANTIANGIOGEN? OR ANTITUMOUR? OR ANTITUMOR? OR ANTIMETAST? OR ANTINEOPLAS? OR ANTICANCER? OR ANTICARCIN?)

L10 44 SEA FILE=HCAPLUS ABB=ON PLU=ON (L3 OR L4) AND ((BOVINE OR COW OR CATTLE)(5A)AORTIC)

L11 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L10 AND ADMIN?

Searcher : Shears 571-272-2528

L12 0 SEA FILE=HCAPLUS ABB=ON PLU=ON L11 AND (PEPTIDE OR PROTEIN OR POLYPROTEIN OR POLYPEPTIDE OR AMINO)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 10:17:49 ON 06 FEB 2004)
L13 4 S L12
L14 1 S L13 NOT L8

L14 ANSWER 1 OF 1 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1999-601204 [51] WPIDS
DOC. NO. CPI: C1999-174961
TITLE: New **peptides** and derived multivalent ligands based on **angiogenic** homology regions, used to **inhibit** or promote **angiogenesis**, e.g. for **treating tumors.**
DERWENT CLASS: B04 C03 D16
INVENTOR(S): BEN-SASSON, S A
PATENT ASSIGNEE(S): (CHIL-N) CHILDRENS MEDICAL CENT; (YISS) YISSUM RES & DEV CO
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9948923	A1	19990930	(199951)*	EN	75
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP					
AU 9931101	A	19991018	(200009)		
US 6121236	A	20000919	(200048)		
US 6235716	B1	20010522	(200130)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9948923	A1	WO 1999-US6246	19990322
AU 9931101	A	AU 1999-31101	19990322
US 6121236	A	US 1998-46985	19980324
US 6235716	B1 Div ex	US 1998-46985	19980324
		US 1999-474743	19991229

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9931101	A	Based on	WO 9948923
US 6235716	B1	Div ex	US 6121236

PRIORITY APPLN. INFO: US 1998-46985 19980324; US 1999-474743 19991229
AN 1999-601204 [51] WPIDS
AB WO 9948923 A UPAB: 19991207
NOVELTY - New **peptides** (I) are the AHR (angiogenic homology region) of TSP (thrombospondin)-4 or angiostatin or subsequences of these with at least 10 **amino** acids (aa).
DETAILED DESCRIPTION - (I) have sequences (S1) and (S2):
RNVGWKDKVSYRWFLQHRPQVGYIRVRFYEGSELV (S1)

ISKTMSGLECQAWDSQSPHAHGYIPSKFPNKNIKK (S2)

INDEPENDENT CLAIMS are also included for the following:

(1) angiogenic **peptide** (Ia) which is not the AHR of TSP-1 (sequence is given in the specification), or its subsequences, containing at least 10 aa from the formula AA1-AA28, where each AA is a specific aa;

(2) angiogenic **peptide** derivatives (Ib) of **peptides** (S3), (S4) or (S5)-(S8);

(3) multivalent ligands of formula (II);

(4) **polypeptide** multivalent ligand of formula (III), and

(5) method for modulating angiogenesis by **administering** (II) or (III):

Ac-TFRAFLSSRLQTGFIRVVMYEG (S3)

Ac-AYRWRLSHRPKDLYSIVRRADG (S4)

Ac-TAYRWRLSHRPKDLYSIVRRADR (S5)

Ac-AYRWRLSHRPKDLYSIVRRADR (S6)

Ac-RWRLSHRPKDLYSIVRRADR (S7)

Ac-KDFTAYRWRLSHRPKDLYSIVRRADR (S8)

B-(-L-P)n (II)

B = multilinker backbone;

n = 2 to about 20;

each L = covalent bond or linking group;

each P = angiogenic **peptide**, at least two being a derivative of AHR or hybrid **peptide** (or its derivative)

P-(S-P)m-S-P (III)

m = 0-20;

each S = **peptide** spacer of 5-30 aa;

each P = **peptide** of 10-40 aa, at least two being as defined in (II).

ACTIVITY - Anti-angiogenic; Angiogenic; **Antitumor**; Anti-arthritic; Anti-obesity; Anti-ulcer.

MECHANISM OF ACTION - Modulation of angiogenesis. The multivalent ligand Tip-18.40 Ac-TAYRWRLSHRPKDLYSIVRRADR (S9) was incubated with A19 **bovine aortic** endothelial cells at various concentrations for 72-80 hours at 37 deg. C. Cell proliferation was then assessed by methylene blue staining; in presence of 20 mu g/ml (S9) the number of cells was only about 40% of that for an untreated control culture.

USE - Multivalent ligands (A) based on (I) and related angiogenic **peptides** may be anti-**angiogenic**, e.g. for **treating tumors**, cardiovascular disease (arteriosclerosis, ischemia), obesity, osteoarthritis, duodenal ulcers, abnormal ocular vascularization in diabetes etc., or they are proangiogenic, e.g. for promotion of wound healing and to stimulate neovascularization around occluded blood vessels (a potential alternative to by-pass surgery or angioplasty). (A) may be used in human or veterinary medicine. (A) may also be used to raise **peptide**-specific antibodies (used for detecting the **peptides**) and to identify and isolate compounds that interact with, and modulate activity of, AHR. Mice were inoculated with 0.2 million B16 melanoma cells (subcutaneously), then injected with 20-30 mg/kg/day (subcutaneously at sites remote from the tumor) of ligand Tip-18.40 of formula Ac-TAYRWRLSHRPKDLYSIVRRADR. Eleven days after **treatment** had started the **tumor** volume was only about 1/3 of that in untreated controls. The ligand of formula Ac-TAYRWRLSHRPKDLYSIVRRADR stimulated tumor growth.

ADVANTAGE - AHR are relatively small, conserved sequences from

different angiogenic **peptides** that are (largely) responsible for biological activity. They are cheaper to prepare than complete **proteins**; may be effective at lower doses; have long-lasting in vivo effect and good biodistribution following oral or parenteral **administration**.
Dwg.0/12

FILE 'HOME' ENTERED AT 10:24:25 ON 06 FEB 2004